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H-28548: COMBINED CHRONIC TOXICITY/ONCOGENICITY STUDY 2-YEAR ORAL GAVAGE STUDY IN RATS

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TEST GUIDELINES:
- U.S. EPA Health Effects Test Guidelines OPPTS 870.4300 Combined Chronic Toxicity/Carcinogenicity (1998)
- OECD Guidelines for the Testing of Chemicals Section 4 (No. 453) Health Effects (2009)
- JMAFF Japan Agricultural Chemicals Regulation Law 12 Nousan No. 8147 (2000)
- EEC Methods for the Determination of Toxicity Method B.33 Combined Chronic/Carcinogenicity test, Directive 88/302/EC (1988)

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Appendix K
Pathology Report

H-28548: COMBINED CHRONIC TOXICITY/ONCOGENICITY STUDY 2-YEAR ORAL GAVAGE STUDY IN RATS

PATHOLOGY REPORT

TEST ARTICLE: H-28548

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STUDY NUMBER: 125-141

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1. MATERIALS AND METHODS

1.1. Macroscopic

Necropsy examinations were performed under procedures approved by a veterinary pathologist on animals euthanized *in extremis* or found dead and on all surviving animals at the scheduled interim and terminal necropsies. The animals were euthanized by carbon dioxide inhalation followed by exsanguination via the abdominal vena cava. The animals were examined carefully for external abnormalities including palpable masses. The skin was reflected from a ventral midline incision and any subcutaneous masses were identified and correlated with antemortem findings. The abdominal, thoracic, and cranial cavities were examined for abnormalities. The organs were removed, examined, and, where required, placed in fixative. The pituitary was fixed *in situ*. All designated tissues were fixed in neutral buffered formalin, except for the eye (including the retina and optic nerve) and testes, which were fixed using a modified Davidson's fixative[1]. Formalin was infused into the lung via the trachea and into the urinary bladder. A full complement of tissues and organs was collected from all animals.

1.2. Organ Weights

Body weights and protocol-designated organ weights were recorded for all surviving animals at the scheduled necropsies and appropriate organ weight ratios were calculated (relative to body and brain weights). Paired organs were weighed together. The thyroid/parathyroid glands were weighed following fixation. A combined weight for the thyroid and parathyroid glands was collected.

1.3. Microscopic

Microscopic examination of fixed hematoxylin and eosin-stained paraffin sections was performed on protocol-designated sections of tissues. The slides were examined by a board-certified veterinary pathologist. A four-step grading system was utilized to define gradable lesions for comparison between dose groups.

1.3.1. Neoplastic Lesions

For fatal and incidental neoplasms, the onset date was considered to be the fate date of the affected animal. For mortality independent neoplasms, the onset date was considered to be the first appearance of a related abnormality (e.g., abrasion, nodule, and/or swelling) that was consistently recorded in the detailed clinical observation data at the site of the neoplasm. The first appropriate mass observation was used as the onset date if no appropriate clinical observations were previously noted for a given neoplasm site. If neither an appropriate clinical observation nor a mass finding could be correlated to a given neoplasm, the onset date was considered to be the fate date of the affected animal.

1.3.2. Peer Review

A pathologist other than the study pathologist performed a formal peer review of the histopathologic findings. This review consisted of an examination of all tissues determined to be target organs by the study pathologist, all neoplasms diagnosed in the study, and all

tissues from 10% of the animals selected randomly from the control and high dose groups. Other selected tissues were examined at the discretion of the reviewing pathologist.

2. RESULTS AND DISCUSSION

The pathology glossary is presented following the narrative. A list of organs and tissues collected, weighed, and examined for this study is presented in Appendix A. The pathology data are presented in Appendix B.

2.1. Unscheduled Deaths

A single test article-related cause of death/moribundity was inflammation/necrosis of the kidneys which occurred in 7 of the 500 mg/kg/day females and was characterized by papillary necrosis. In males the most common cause of death moribundity were pituitary tumors and undetermined. In females the most common causes of death/moribundity were mammary tumor and pituitary tumor.

2.2. Macroscopic

Interim

A test article-related macroscopic observation, "irregular surface" of the kidneys, was noted in the kidneys of one 500 mg/kg/day (high dose) female (animal number 1561). This observation correlated with mild chronic progressive nephropathy in this animal and was indicative of a slight increase in severity of chronic progressive nephropathy in the 500 mg/kg/day female group at one year. Other macroscopic observations were considered incidental and typical of lesions seen in rats of this strain and age.

Terminal

No test article-related macroscopic observations were noted in males. In females, test article-related macroscopic observations were noted in the kidneys and liver. In the kidneys, "irregular surface" was noted in 16 of 70 animals at 500 mg/kg/day (not present in controls or any of the lower dose groups), while in the liver, "tan focus/foci" was noted in 1, 1, 1, 8 of 70 animals each at 0, 1, 50, and 500 mg/kg/day, respectively, and "mass/nodule" was noted in 14 of 70 animals at 500 mg/kg/day (not present in controls or any of the lower dose groups). These macroscopic observations were correlative to test article-related microscopic findings described below.

2.3. Organ Weights

Interim

Test article-related organ weight changes were limited to the high dose groups. Increased liver weights occurred in males at 50 mg/kg/day and in females rats at 500 mg/kg/day. In males, the increase was small and only the mean liver relative to body weight was statistically significantly increased (14.53% above control). In females, the liver weight increase was larger (mean liver relative to body weight was 66.75% above control) and all parameters (absolute and relative to both brain and body weight) were statistically significantly increased. The liver weight changes in the affected male and female groups were associated with microscopic changes in the liver (discussed below).

Mean final body weight at the interim necropsy was 19.51% less than control in the 500 mg/kg/day females. As a result of this decrement in mean final body weight, the brain, kidney, and thyroid/parathyroid relative to body weight were statistically significantly increased. Aside from a slight increase in severity of chronic progressive nephropathy in the kidneys, there were no microscopic changes in these organs associated with the increased weights, and mean absolute weights were not increased. Thus, these changes were considered secondary to the body weight decrement at 500 mg/kg/day. Additionally, mean absolute and relative to brain weights of the spleen in the 500 mg/kg/day females were statistically significantly lower than controls. These differences were not considered test article-related, as there were no microscopic changes in the spleen in either sex.

Terminal

No test article-related or statistically significant organ weight changes occurred in males.

In females, the only test article-related effect on organ weights was an increase in liver weights at 500 mg/kg/day. Mean absolute and relative to both body and brain weights were increased compared to control, with mean liver relative to body weight 41.61% greater than control. There were several test article-related microscopic changes to account for the increased weights, as described below.

2.4. Microscopic

Interim

Test article-related microscopic findings were noted in the liver of both male and female rats, and in the kidneys of females, in the high-dose groups (50 and 500 mg/kg/day for males and females, respectively).

In males, there was a slight increase in minimal focal cystic degeneration of the liver (0, 0, 0, 3 at 0, 0.1, 1, and 50 mg/kg/day, respectively). This finding was more pronounced in the terminal portion of the study. Also in males, there was a slight increase in minimal to mild focal necrosis of the liver (1, 1, 0, 5 at 0, 0.1, 1, and 50 mg/kg/day, respectively).

In females, the only microscopic finding in the liver was centrilobular hypertrophy, which occurred in all 10 of the 500 mg/kg/day females. This change was of minimal severity and was characterized primarily by a slight increase in size of centrilobular hepatocytes with increased red granularity to the cytoplasm and is consistent with peroxisome proliferation. Also in females, there was a very slight increase in incidence and severity of chronic progressive nephropathy in the kidneys at 500 mg/kg/day. This change was characterized by foci of basophilic tubules, some with thickening of basement membranes. In the 500 mg/kg/day group, most incidences were of mild severity, while in the other groups, including controls, the incidences were primarily of minimal severity, although in a single control female the incidence was of moderate severity.

Incidences And Severity of Chronic Progressive Nephropathy in the Kidneys of Female Rats: Interim Sacrifice				
Dose level: mg/kg/day	**0**	**1**	**50**	**500**
Kidney				
Nephropathy, chronic progressive	6	4	6	9
-minimal	5	3	4	3
-mild	0	1	2	6
-moderate	1	0	0	0

In males, there was a single interstitial cell adenoma of the testes at 50 mg/kg/day; incidences of interstitial cell hyperplasia were 1, 0, 0, 3 at 0, 0.1, 1, and 50 mg/kg/day. The incidences of these changes in treated groups were not statistically different from controls (historical data for rats of this age were not available). Proliferative interstitial cell lesions are discussed in more detail under microscopic findings for the terminal sacrifice. All other microscopic findings were considered incidental, and typical of those seen in rats of this strain and age.

Terminal

Non-neoplastic

Test article-related non-neoplastic microscopic changes were observed in the liver of males and in the liver, kidneys, nonglandular stomach (limiting ridge), and tongue of females at the highest doses tested, 50 mg/kg/day in males and 500 mg/kg/day in females.

Liver

In the liver of males at 50 mg/kg/day there were statistically significantly increased incidences of focal cystic degeneration, centrilobular hepatocellular hypertrophy, and centrilobular hepatocellular necrosis. Cystic degeneration was characterized by the presence of multilocular cystic spaces containing finely granular or flocculent material without endothelial or epithelial cells lining the spaces. Centrilobular hypertrophy, morphologically consistent with peroxisome proliferation, was characterized by hepatocytes with red granular cytoplasm sometimes containing small amounts of pigment morphologically compatible with lipofuscin. Centrilobular hepatocellular necrosis was typically of the coagulative type with strongly eosinophilic-staining cytoplasm and pyknotic nuclei.

Test article-related findings in the liver of females at 500 mg/kg/day were similar to those noted in males at 50 mg/kg/day, and also included low incidences of panlobular hepatocellular hypertrophy and individual cell hepatocellular necrosis. Panlobular hepatocellular hypertrophy was characterized by enlargement of hepatocytes (as described above for centrilobular hypertrophy) throughout the entire liver. Individual cell necrosis was characterized by the presence of scattered single hepatocytes with features characteristic of apoptosis.

Summary of Selected Non-neoplastic Findings in the Liver of Male and Female Rats				
Dose level: mg/kg/day	**0**	**0.1**	**1**	**50**
Male				
Degeneration, cystic, focal	24/70 (34.29%)	24/70 (34.29%)	19/70 (27.14%)	42/70#* (60.00%)
Hypertrophy, hepatocyte, centrilobular	0/70 (0.00%)	0/70 (0.00%)	0/70 (0.00%)	7/70#* (10.00%)
Necrosis, hepatocytes, centrilobular	1/70 (1.43%)	0/70 (0.00%)	1/70 (1.43%)	5/70# (7.14%)
Dose level: mg/kg/day	**0**	**1**	**50**	**500**
Female				
Degeneration, cystic, focal	2/70 (2.86%)	2/70 (2.86%)	2/70 (2.86%)	14/70#* (20.00%)
Hypertrophy, hepatocyte, centrilobular	0/70 (0.00%)	0/70 (0.00%)	3/70 (4.29%)	65/70#* (92.86%)
Hypertrophy, hepatocyte, panlobular	0/70 (0.00%)	0/70 (0.00%)	0/70 (0.00%)	3/70# (4.29%)
Necrosis, hepatocytes, centrilobular	1/70 (1.43%)	1/70 (1.43%)	4/70 (5.71%)	7/70# (10.00%)
Necrosis, individual hepatocyte	0/70 (0.00%)	0/70 (0.00%)	0/70 (0.00%)	3/70# (4.29%)
# - Statistically significant by Cochran-Armitage trend test ($p<0.05$)				
* - Statistically significant by Fisher's exact test ($p< 0.05$)				

Kidneys

Statistically significantly increased microscopic findings in the kidneys of females at 500 mg/kg/day included tubular dilatation, edema of the renal papilla, transitional cell hyperplasia in the renal pelvis, tubular mineralization, renal papillary necrosis, and chronic progressive nephropathy. Tubular dilatation frequently occurred in an ascending pattern extending from the papilla to the outer cortex, while at other times it was more prominent in the papilla. Edema of the papilla was characterized by increased rarefaction or myxomatous change in the papillary interstitium, sometimes with polypoid protrusions from the lateral surface of the papilla. The edema and tubular dilatation were often associated with hyperplasia of the transitional cell epithelium lining the papilla and pelvis. In some animals, necrosis of the tip of the papilla was present. In some 500 mg/kg/day females with the renal papillary changes, lesions diagnosed as chronic progressive nephropathy (CPN) were comprised of dilated tubules (often in an ascending pattern as described above), mononuclear cell infiltrates, and basophilic tubules, but with less thickening of tubular basement membranes than typically seen in CPN. In these animals, the constellation of lesions

diagnosed as CPN may be more representative of retrograde nephropathy as described by Hard, et al.[2], rather than typical CPN.

Summary of Selected Non-neoplastic Findings in the Kidneys of Female Rats				
Dose level: mg/kg/day	**0**	**1**	**50**	**500**
Dilatation, tubular	4/70 (5.71%)	2/70 (2.86%)	5/70 (7.14%)	28/70#* (40.00%)
Edema, papilla	4/70 (5.71%)	1/70 (1.43%)	2/70 (2.86%)	43/70#* (61.43%)
Hyperplasia, transitional cell	6/70 (8.57%)	3/70 (4.29%)	12/70 (17.14%)	33/70#* (47.14%)
Mineralization, tubular	25/70 (35.71%)	32/70 (45.71%)	28/70 (40.00%)	42/70#* (60.00%)
Necrosis, papillary	0/70 (0.00%)	0/70 (0.00%)	0/70 (0.00%)	16/70#* (22.86%)
Nephropathy, chronic progressive	39/70 (55.71%)	40/70 (57.14%)	41/70 (58.57%)	64/70#* (91.43)
# - Statistically significant by Cochran-Armitage trend test ($p<0.05$) * - Statistically significant by Fisher's exact test ($p< 0.05$)				

The nonglandular stomach (limiting ridge only) and the tongue had statistically significantly increased incidences of hyperplasia of squamous epithelium at 500 mg/kg/day. In the tongue, subacute/chronic inflammation occurred in association with squamous epithelial cell hyperplasia. There is no data describing incidence of epithelial hyperplasia of the limiting ridge of the nonglandular stomach in the historical control database for 2 year studies. The incidence of squamous cell hyperplasia of the tongue at 500 mg/kg/day (18.6%) exceeds the historical control range of 0-3.3%.[3] There was also a single incidence of squamous cell carcinoma (1.4%) in the tongue of females at 500 mg/kg/day. This is well within the historical control range of 0-1.7%[4] and the finding of a single such tumor was not considered a direct result of test article administration.

Summary of Selected Non-neoplastic Findings in the Nonglandular Stomach and Tongue of Female Rats				
Dose level: mg/kg/day	**0**	**1**	**50**	**500**
Stomach, nonglandular				
Hyperplasia, epithelial, limiting ridge	0/70 (0.00%)	0/70 (0.00%)	0/70 (0.00%)	9/70#* (12.86%)
Tongue				
Hyperplasia, squamous cell	2/70 (2.86%)	8/70 (11.43%)	4/70 (5.71%)	13/70#* (18.57%)
Inflammation, subacute/chronic	3/70 (4.29%)	8/70 (11.43%)	4/70 (5.71%)	13/70#* (18.57%)
# - Statistically significant by Cochran-Armitage trend test ($p<0.05$) * - Statistically significant by Fisher's exact test ($P < 0.05$)				

Other

A statistically significant increase in the incidence of alveolar histiocytosis was present in females at 500 mg/kg/day. The incidences were 22, 20, 21, 42 (61%) at 0, 1, 50, and 500 mg/kg/day, respectively. The incidence at 500 mg/kg/day was statistically significant by both the Fisher Exact test and the Cochran-Armitage trend test and is at the upper end of the historical control range of 9.2-61.7%.[3] The increased incidence of this common background finding may be secondary to aspiration of dosing formulation at this high concentration; however, a definitive mechanism for this increase could not be determined.

A slight but statistically higher (by the Cochran-Armitage Trend test) incidence of pancreatic acinar cell hyperplasia occurred in females at 50 and 500 mg/kg/day; incidences were 0, 2, 5, 5 (7.1%) at 0, 1, 50, and 500 mg/kg/day, respectively. The incidences of acinar cell hyperplasia at the two highest doses slightly exceeded the historical control range of 0-4.6%[3], but were not significant by the Fisher Exact test and were not associated with pancreatic acinar cell tumors. In addition, acinar cell hyperplasia did not occur in a clear dose response manner, as incidences in the 50 and 500 mg/kg/day groups were the same despite the order of magnitude difference in dose. In contrast, all other test article-related changes observed at 500 mg/kg/day occurred with a clear dose response. Therefore, the slight increase in acinar cell hyperplasia in the 50 and 500 mg/kg/day females was considered most likely spurious and not test article-related.

A statistically significant increase (by both the Fisher Exact test and the Cochran-Armitage trend test) in the incidence of alopecia/hypotrichosis was present in females at 500 mg/kg/day. The incidences were 1/70, 2/48, 5/55, and 9/70 (12.9%). However, the relevance of alopecia/hypotrichosis is more appropriately made by interpretation of the incidence of this finding in the clinical observations of the study rather than the microscopic

observations. Therefore, for microscopic purposes, this was not considered at potential target organ.

Finally, incidences of cataract of the lens of the eye, pelvic mineralization of the kidney, and angiectasis of the liver were statistically significantly increased. Cataract of the eye and angiectasis of the liver were statistically significantly increased by the Cochran-Armitage trend test at 500 mg/kg/day while pelvic mineralization of the kidney was statistically significantly increased by the Cochran-Armitage trend test and Fisher's exact test at 500 mg/kg/day, and Fisher's exact test at 1 mg/kg/day. Incidences of cataract of the eye were 0/69, 0/48, 0/55, and 3/70 (4.29%) at 0, 1, 50, and 500 mg/kg/day, respectively. The historical control range for cataract is 0 to 10.8%.[3] Incidences of pelvic mineralization of the kidney were 52/70, 63/70, 58/70, and 63/70 (90.0%) at 0, 1, 50, and 500 mg/kg/day, respectively. The historical control range is 45.0 to 87.7% (note: two studies in the historical control database with an incidence of 0/60 reflect that this change was simply not tracked as pelvic mineralization in the studies).[3] Incidences of angiectasis of the liver were 1/70, 0/70, 3/70, and 5/70 (7.14%) at 0, 1, 50, and 500 mg/kg/day, respectively. The historical control range is 0 to 10.0%.[3] For each of the changes, the incidence was well within the historical control range, except pelvic mineralization, which is a very common background finding, only slightly exceeded the historical control range. Thus, these changes were not considered test article-related.

All other non-neoplastic microscopic observations were of the type typically seen in rats of this strain and age, and were considered incidental and not related to test article administration.

Neoplastic

Test article-related neoplastic changes occurred in the liver of females administered 500 mg/kg/day, the highest dose tested in females. Equivocal increases in pancreatic acinar cell tumors and testicular interstitial (Leydig) cell tumors occurred in males administered 50 mg/kg/day, the highest dose tested in males.

Liver

In females, hepatocellular adenoma occurred with an incidence of 0, 0, 0, and 11 (15.71%) at 0, 1, 50, and 500 mg/kg/day, respectively (statistically significant by the pairwise Fisher Exact test, the Cochran-Armitage trend test and the Peto test). Hepatocellular carcinoma occurred with an incidence of 0, 0, 0, 4 (5.71%) at 0, 1, 50, and 500 mg/kg/day, respectively (statistically significant by the Cochran-Armitage trend test and the Peto test, but not the Fisher Exact test). The incidences of both adenoma and carcinoma exceeded the historical control range (hepatocellular adenoma: 0-5.0%; hepatocellular carcinoma: 0-1.7%).[4] The increased incidences of hepatocellular tumors in the 500 mg/kg/day female group occurred in association with degenerative/necrotic changes in the liver at this dose level (see above under discussion of non-neoplastic lesions).

No hepatocellular tumors were observed in females administered 1 or 50 mg/kg/day, and no test article-related degenerative or necrotic changes occurred in the livers at these concentrations. Few hepatocellular tumors occurred in males and the incidence was

essentially no different between the controls and the 50 mg/kg/day group, the highest dose tested. Hepatocellular adenomas occurred with an incidence of 1, 2, 1, 1 at 0, 0.1, 1, and 50 mg/kg/day, respectively, while hepatocellular carcinoma occurred with an incidence of 1, 0, 0, 2 at 0, 0.1, 1, and 50 mg/kg/day, respectively.

Pancreas

In males, the only statistically significant increase in any tumor type occurred in the pancreas. In high-dose males administered 50 mg/kg/day, the incidences of pancreatic acinar cell adenoma/carcinoma combined—but not adenoma or carcinoma alone—were statistically significantly increased. Incidences of pancreatic acinar cell adenoma were 0, 1, 0, 3 (4.29%) at 0, 0.1, 1, and 50 mg/kg/day, respectively. The increased incidence at 50 mg/kg/day was not statistically significant by either the Cochran-Armitage trend test, the Peto test, or the pairwise Fisher Exact test, and was within the laboratory historical control range of 0-5.0%.[4] Two carcinomas (2.86%) were also observed in the 50 mg/kg/day male group (not statistically significant but slightly outside the historical range of 0-1.7%)[4], so the incidences of adenoma/carcinoma combined were 0, 1, 0, 5, respectively. The combined incidence of adenoma and carcinoma (5/70) at 50 mg/kg/day was significant by both the Cochran-Armitage trend test and the Peto test but not by the Fisher Exact test.

Since pancreatic acinar cell hyperplasia and adenoma in rats occur along a continuum, the incidence of acinar cell hyperplasia is also expected to be increased when a test-article related increase in acinar cell adenoma is observed. However, the incidences of acinar cell hyperplasia were not significantly different from controls in any of the treated male groups (incidences of acinar cell hyperplasia were 16, 18, 7, 21 at 0, 0.1, 1, and 50 mg/kg/day, respectively).

In summary, the incidences of acinar cell adenoma/carcinoma combined in the 50 mg/kg/day male group were statistically increased and slightly outside historical controls, but were not associated with statistically significant increases in either acinar cell adenoma or carcinoma alone nor with increases in acinar cell hyperplasia. Based on these considerations, and the known PPARα agonist activity of the test article, the marginal increase in pancreatic acinar cell tumors in the 50 mg/kg/day male group provides equivocal evidence of a test article-related effect.

Testes

The incidences of interstitial cell adenoma of the testes were 4, 4, 1, 8 (11.43%) at 0, 0.1, 1, and 50 mg/kg/day in the male groups, respectively (as noted above, an interstitial cell adenoma was also present in one male in the 50 mg/kg/day group at the interim sacrifice). These incidences were not statistically significant by the pairwise Fisher Exact test, the Cochran-Armitage trend test or the Peto test, but slightly exceeded the historical control range of 0-8.3%.[4] The incidences of interstitial cell hyperplasia were 7, 7, 3, 15 (21.4%) at 0, 0.1, 1, and 50 mg/kg/day, respectively. These incidences of hyperplasia were also not statistically significant by pairwise or trend analysis. The laboratory historical range for interstitial cell hyperplasia is 0-8.3% (the same as that for adenoma).[3] Thus, in the current study, the incidences of interstitial cell hyperplasia in both treated and control groups (with the exception of the 1 mg/kg/day group) exceeded the historical range.

Since PPARα agonists are known to produce proliferative interstitial cell lesions (hyperplasia and adenoma) in the testes of rats, a relationship to treatment for these findings in the 50 mg/kg/day male group cannot be ruled out. However, based on the marginal nature of the increased incidences of these lesions, their lack of statistical significance, and the relatively high incidence of these lesions in concurrent controls, the relationship to treatment for these findings is equivocal. There were no test article-related increases in proliferative interstitial cell lesions of the testes in the 0.1 and 1 mg/kg/day groups, as the incidences of interstitial cell tumors and hyperplasia were similar to or less than controls in the 0.1 and 1 mg/kg/day groups.

Other
All other statistically significant increases in neoplastic lesions occurred in females and were considered to represent the spontaneous occurrence of neoplasms commonly seen in rats of this strain and age.

Uterine stromal polyps occurred with an incidence of 1, 2, 1, 7 (10.0%) for 0, 1, 50, and 500 mg/kg/day, respectively. The increased incidence at 500 mg/kg/day was statistically significant by the Cochran-Armitage trend test and the Peto test, but was not statistically significant by the Fisher Exact test and was well within the historical control range of 0-13.8%.[4] Therefore, this finding was not considered to be test article-related.

Finally, adenoma of the pars distalis of the pituitary gland was statistically increased by the pairwise Fisher Exact test at 1 and 50 mg/kg/day. These increases did not occur in a dose-related manner, as the incidence of pituitary adenoma in 500 mg/kg/day females was not statistically different from controls. In addition, the incidence of this tumor in all groups was within the laboratory historical range of 59.2-91.1%.[4] Pars distalis adenomas occurred with an incidence of 53/70 (75.71%), 58/65 (89.23%), 58/65 (89.23%), 52/70 (74.29%) at 0, 1, 50, and 500 mg/kg/day, respectively. Thus, since the incidences at 1 and 50 mg/kg/day are within the historical control range and are also not dose-related, they were not considered test article-related. Further, when the incidence of pituitary gland adenoma and carcinoma are combined there is no statistical significance at any dose.

No other tumor types were statistically significantly increased in either sex.

The test article belongs to a class of compounds known as peroxisome proliferators (PPARα agonists)[5], which are known to produce liver, pancreatic, and testicular tumors in rats, and liver tumors in mice.[6,7] However, these compounds have not been shown to be carcinogenic in other species, including humans.[7,8] Based on extensive research into the comparative biology of peroxisome proliferator-induced hepatic carcinogenesis, the induction of liver tumors in rodents by non-genotoxic peroxisome proliferators is not considered relevant to humans.[8,9,10] Furthermore, while less definitive mechanistic data are available on the role PPARα in the induction of pancreatic acinar cell tumors in rats, the available data on a proposed mode of action involving altered bile flow and increased cholecystokinin (CCK) suggest that this mode of action is also likely not relevant to humans.[10] Mechanistic data on the mode of action for induction of testicular interstitial cell tumors in rats by peroxisome

proliferators is less robust.[10] However, extensive research into the comparative biology and mechanisms of action of interstitial cell tumor induction in rodents by a wide class of non-genotoxic compounds indicate that these tumors most likely have low relevance to humans under most exposure condition.[11,12]

3. PATHOLOGY CONCLUSIONS

Following oral (gavage) exposure of male and female rats to the test article for up to two-years, test article-related changes in pathology parameters were limited to the high dose groups (50 and 500 mg/kg/day in males and females, respectively). Non-neoplastic changes occurred in the kidneys, liver, squamous regions of the gastrointestinal tract, and lung of 500 mg/kg/day females, and in the liver of 50 mg/kg/day males. Neoplastic (and/or hyperplastic) changes included hepatocellular tumors in 500 mg/kg/day females and, equivocally, pancreatic acinar cell tumors and testicular interstitial cell tumors in 50 mg/kg/day males. All tumors occurred with a clear dose-related threshold, as no hepatocellular tumors were observed in females at lower doses, the only pancreatic acinar cell tumor that occurred below 50 mg/kg/day was an adenoma that occurred at 0.1 mg/kg/day (not dose-related and well within the historical control range of 0-5.0%[4]), and the incidences of interstitial cell tumors and hyperplasia in males at lower doses were less than or equal to those of controls. In females, liver tumors occurred in association with marked systemic toxicity, as well as liver toxicity.

The induction of liver tumors in female rats at 500 mg/kg/day, and the equivocal increase in pancreatic acinar and testicular interstitial cell tumors in male rats at 50 mg/kg/day are likely not relevant to humans based on the following: most research indicates that induction of these specific tumors in rats by non-genotoxic peroxisome proliferators likely has little or no relevance to humans, especially in plausible human exposure scenarios; the test material was determined to be non-genotoxic based on a battery of *in vivo* and *in vitro* genotoxicity studies; liver tumors were produced only in females and only at doses associated with marked hepatic and systemic toxicity (including lethality); and thresholds were established for all tumor types.

No adverse pathology findings occurred in male rats administered 0.1 or 1 mg/kg/day or in females administered 1 or 50 mg/kg/day

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PATHOLOGY GLOSSARY

Grading System:

Minimal - The amount of change present barely exceeds that which is considered to be within normal limits.

Mild - In general, the lesion is easily identified but of limited severity. The lesion probably does not produce any functional impairment.

Moderate - The lesion is prominent but there is significant potential for increased severity. Limited tissue or organ dysfunction is possible.

Severe - The degree of change is either as complete as considered possible or great enough in intensity or extent to expect significant tissue or organ dysfunction.

Abrasion/scab - Presence of a skin scrape or excoriation usually covered with a scab or crust (dried pus and blood).

Abscess - An inflammatory reaction characterized by a circumscribed accumulation of neutrophils (pus). The reaction may be caused by an infectious process, such as bacteria, or by a non-infectious process, such as foreign material or tissue irritation.

Absent - Not present, missing.

Absent/broken/malocclusion/ overgrown - A diagnosis used exclusively to describe dental abnormalities which includes the most common deviations from normal seen involving the teeth, particularly in rats and mice. Any or all of the conditions may apply in any given instance.

Absent/cannibalized – The missing organ has been eaten by cage mates.

Absent portion/cannibalized - A portion of a tissue is absent or missing due to cannibalization by cagemates.

Absent, portion - Missing a part of the whole.

Adenocarcinoma - A malignant epithelial neoplasm in which the cells form recognizable glandular structures or in which the cells are clearly derived from glandular epithelium.

Adenocarcinoma (primary site unknown) - A malignant tumor of the glandular epithelium for which the organ of origin cannot be determined.

Adenoma - A benign epithelial neoplasm in which the cells form recognizable glandular structures or in which the cells are clearly derived from glandular epithelium.

Adenoma, acinar cell - A benign neoplasm of acinar cell origin.

Adenoma, basal cell - A benign epithelial neoplasm arising from the keratinocytes present in the basal layer of the epidermis (basal cells).

Adenoma, C-cell - A benign epithelial neoplasm arising from the C-cells of the thyroid gland.

PATHOLOGY GLOSSARY

Adenoma, cortical - A benign neoplasm derived from cells of the adrenal cortex. It is characterized by a well-demarcated mass of cortical cells with loss of normal cortical architecture and compression of adjacent parenchyma.

Adenoma, follicular cell - A benign epithelial neoplasm arising from the thyroid follicular cells.

Adenoma, hepatocellular - A benign epithelial neoplasm arising from hepatocytes.

Adenoma, interstitial cell - A benign neoplasm arising from interstitial cells (Leydig cells) of the testes.

Adenoma, islet cell - A benign epithelial neoplasm arising from islet cells of the pancreas.

Adenoma, pars distalis - A benign neoplasm arising from the cells of the pars distalis of the pituitary gland.

Adenoma, sebaceous cell - A benign epithelial neoplasm arising from sebaceous glands or showing sebaceous differentiation.

Adenoma, tubular cell - A benign neoplasm arising from renal tubule cells.

Adhesion - The binding together of adjacent organs or tissues by cells or cell products. The adhesions may be formed from the proliferation of fibroblasts with collagen production, from fibrin exuded in response to an irritant, or from the presence of fibrin on the serosal surface of the adhered organs or tissues.

Alopecia/hypotrichosis - The skin has fewer than normal hair shafts and/or hair follicles.

Angiectasis - The dilatation of a blood or lymphatic vessel or sinusoid.

Angiectasis/cystic degeneration, focal cortical - Focal degenerative changes in the adrenal cortex that result in variably sized cystic spaces that may be blood-filled and may include the dilatation of a blood or lymphatic vessel or sinusoid.

Astrocytoma, malignant - A malignant neoplasm of the central nervous system composed of neuroglial cells of ectodermal origin (astrocytes).

Atrophy - A wasting away or decrease in the size of a cell, tissue, organ, or part.

Atrophy, acinar - A decrease in the size of acini, which are small sac-like dilatations found in various glands.

Atrophy, cortical - Thinning of the adrenal cortex which is generally diffuse and attributable to diminished cell size and probable loss of some cells.

Bacterial colonies - An aggregate or cluster of bacteria of apparently similar lineage.

Body fat depleted - The loss of visible fat from the body, especially in subcutaneous tissue, retroperitoneal space, abdominal cavity and/or mediastinum.

Calculus/calculi - The formation of one or more mineralized concretions within the lumen and/or collecting space of an organ.

PATHOLOGY GLOSSARY

Carcinoma, acinar cell - A malignant neoplasm of the pancreatic acinar cells.

Carcinoma, C-cell - A malignant epithelial neoplasm arising from C-cells of the thyroid gland.

Carcinoma, cortical - A malignant neoplasm derived from cells of the adrenal cortex.

Carcinoma, follicular cell - A malignant epithelial neoplasm arising from thyroid follicular cells.

Carcinoma, hepatocellular - A malignant epithelial neoplasm arising from hepatocytes.

Carcinoma, islet cell - A malignant epithelial neoplasm arising from the islet cells of the pancreas.

Carcinoma, pars distalis - A malignant neoplasm of cells from the pars distalis.

Carcinoma, sebaceous cell - A malignant epithelial neoplasm arising from sebaceous glands or showing sebaceous differentiation.

Carcinoma, sebaceous cell (primary site unknown) - A malignant epithelial neoplasm arising from sebaceous glands or showing sebaceous differentiation. The primary site is unknown.

Carcinoma, squamous cell - A malignant epithelial neoplasm arising from squamous epithelium or showing squamous differentiation.

Carcinoma, tubular cell - A malignant neoplasm originating from the renal tubular epithelium.

Cardiomyopathy - A degenerative myocardial disease, often of obscure or unknown etiology, characterized by infiltration of lymphocytes, degeneration and/or loss of myocardial cells, and/or fibrosis.

Cataract - Macroscopically, an opacity of the lens of the eye. Histologically, corresponding findings in the lens can include irreversible swelling, degeneration, fragmentation, and liquifaction of the lens fibers with or without hyperplasia of the lens epithelium.

Cloudy - Dimmed or dulled, uneven in color or transparency, an opaque change in an otherwise transparent structure or medium (e.g. the lens, cornea, or humor of the eye).

Compression, ventral (pituitary tumor) - Compression of brain or spinal cord neuropil caused by a pituitary tumor.

Congestion - The excessive or abnormal accumulation of blood within the vessels of an organ or tissue.

Congestion, chronic passive - In the liver, there is dilatation of centrilobular and mid-zonal sinusoids with compression of intervening hepatic cords. In the lung**,** alveolar walls are thickened and many alveoli contain hemosiderin laden macrophages and proteinaceous material. These diffuse liver and lung lesions are a result of markedly obtunded blood flow through the heart.

PATHOLOGY GLOSSARY

Crust, **serocellular** - A layer of mixed material adhered to the epidermal surface composed of cornified epithelium, serum, inflammatory cells, and necrotic cell fragments.

Crystals, hemoglobin - Accumulation within a tissue of rod-shaped crystals, from the iron-containing heme and globulin of hemoglobin.

Cyst - Any closed cavity or sac usually containing a liquid or semisolid material and often lined by epithelium.

Cyst, biliary, multiloculated – A cavity or sac of the bile ducts or the gallbladder containing several compartments formed by membranous septa and lined by epithelial cells.

Cyst, biliary, simple – A cavity or sac of the bile ducts or the gallbladder lined by a single layer of epithelial cells.

Cyst, capsule - A round oval space lined by a thin tissue wall is within or attached to the serosa and/or capsule of a tissue.

Cyst, follicular - A follicle that is much beyond the size of the largest follicles normally present in the thyroid. It is lined by low cuboidal follicular cells and is distended by colloid.

Cyst, keratin - Any closed cavity or sac lined by stratified squamous keratinizing epithelium and distended with sloughed keratin.

Degeneration - The deterioration or change of a tissue, organ, or cell to a less functionally active form, including cytoplasmic and/or nuclear changes such as vacuolation, chromatin changes, cell swelling, and/or tinctoral shifts; this is evidence of cell injury.

Degeneration, axonal/myelin - There is discontinuity of the axon and/or myelin sheath. A macrophage or degenerate remnants of axon or myelin may be present.

Degeneration, cystic, focal - A severe form of vacuolar change characterized by cell loss and formation of cystic spaces. In the liver, these spaces are not lined by endothelial cells as epithelial cells and they replace hepatocellular plates.

Degeneration/atrophy, retina, bilateral - Degeneration (cell injury) and/or atrophy (decreased size of cells or decreased thickness of one or more layers) of the retinas of both eyes. In the degenerative stage of retinal injury, histologic evidence of nuclear cytoplasmic damage may be seen, especially in the pigment epithelium or photoreceptor cells. Inflammation may develop, characterized mainly by macrophage influx and phagocytosis of cell debris. By the time atrophy is diagnosed, no ongoing cell injury is evident. Fewer cells are present in the retina and this is usually manifested as loss of cells in the photoreceptor layer.

PATHOLOGY GLOSSARY

Degeneration/atrophy, retina, unilateral - Degeneration (cell injury) and/or atrophy (decreased size of cells or decreased thickness of one or more layers) of the retina of one eye. In the degenerative stage of retinal injury, histologic evidence of nuclear or cytoplasmic damage may be seen, especially in the pigment epithelium or photoreceptor cells. Inflammation may develop, characterized mainly by macrophage influx and phagocytosis of cell debris. By the time atrophy is diagnosed, no ongoing cell injury is evident. Fewer cells are present in the retina and this is usually manifested as loss of cells in the photoreceptor layer.

Degeneration/atrophy, seminiferous tubules, bilateral - In both testes, focal or diffuse deterioration of the tubules in which the spermatozoa develop, usually characterized by reduced cellularity, loss of spermatogenesis, cytoplasmic vacuolation of sustentacular cells, formation of multinucleated syncytial or giant cells, loss of cell layers, and/or intraluminal cellular debris. Changes progress to atrophy when tubules contain few or no germinal cells.

Degeneration/atrophy, seminiferous tubules, unilateral - In one testis, focal or diffuse deterioration of the tubules in which the spermatozoa develop, usually characterized by reduced cellularity, loss of spermatogenesis, cytoplasmic vacuolation of sustentacular cells, formation of multinucleated syncytial or giant cells, loss of cell layers, and/or intraluminal cellular debris. Changes progress to atrophy when tubules contain few or no germinal cells.

Degeneration/necrosis, cartilage - Morphological changes in the chrondrocytes and intercellular matrix of cartilage ranging from degeneration with change in size and tinctorial properties of the cytoplasm and/or nuclei to cell death characterized by loss of cytoplasm, nuclei, and cell contours.

Degeneration/necrosis, myofiber - Changes occurring in muscle which may include any or all of the following: swelling, loss of striations, hyalinization or fragmentation of the individual fibers, proliferation of the sarcolemmal nuclei, and interstitial accumulation of acute or chronic inflammatory cells.

Degeneration/necrosis, olfactory epithelium - Morphologic changes in the olfactory sensory cells ranging from degeneration with a change in size and tinctorial properties of the cytoplasm and/or nuclei to cell death characterized by loss of cytoplasm, nuclei, and cell contours.

Degeneration/regeneration - A spectrum of changes indicative of both cell deterioration and cell repair, including cytoplasmic vacuolation, swelling and/or tinctorial shifts indicating degeneration with increased cytoplasmic basophilia and cellular proliferation indicative of regeneration.

PATHOLOGY GLOSSARY

Degeneration/regeneration, myofiber - A spectrum of changes in the cytoplasm and/or nuclei of muscle fibers within skeletal, cardiac, or smooth muscle tissue, indicative of both cell deterioration and cell repair. Changes include, but are not limited to, cytoplasmic vacuolation, swelling and/or tinctorial shifts indicating degeneration with increased cytoplasmic basophilia and cellular proliferation indicative of regeneration.

Depletion, lymphoid, generalized - An absolute or relative reduction in the number of lymphocytes in all compartments of a lymphoid tissue.

Depletion, secretory - The amount of secretory product in the glands and/or lumen is diminished but lining cells are normal.

Detachment, retinal - Loss of apposition between the sensory retina and the retinal pigmented epithelium.

Dilatation - An increase in size of a tissue or organ due to an expansion of a lumen or other such space or chamber.

Dilatation, cystic, bile ducts - Bile ducts are so dilated as to approximate cysts.

Dilatation, duct - An expansion of the lumen of the ductal elements within a glandular tissue or organ.

Dilatation, gland/lumen - Either individual gland lumens are increased in diameter or the lumen of the organ is dilated.

Dilatation/inflammation - Increased organ size due to dilation or expansion of a lumen or other space with gas, fluid, or secretory product with or without an infiltration of inflammatory cells.

Dilatation, pelvic - An increase in the size of the pelvic space of the kidney; hydronephrosis.

Dilatation, seminiferous tubules, bilateral - In both testes, tubules are dilated but seminiferous epithelium is normal.

Dilatation, seminiferous tubules, unilateral - In one testis, tubules are dilated but seminiferous epithelium is normal.

Dilatation, sinusoidal - The width of hepatic sinusoids is increased.

Dilatation, sinus - The width of lymph node sinuses is increased.

Dilatation, tubular - An expansion of the lumen of tubular elements within a tissue or organ.

Discoloration, brown - A change in color from normal or from surrounding tissue to a brownish hue.

Discoloration, gray - A change in color from normal or from surrounding tissue to a grayish hue.

Discoloration, green - A change in color from normal or from surrounding tissue to a greenish hue.

PATHOLOGY GLOSSARY

Discoloration, pink - A change in color from normal or from surrounding tissue to a pinkish hue.

Discoloration, red - A change in color from normal or from surrounding tissue to a reddish hue.

Discoloration, tan - A change in color from normal or from surrounding tissue to a yellowish-brown hue.

Discoloration, white - A change in color from normal or from surrounding tissue to a whitish or pale hue.

Discoloration, yellow - A change in color from normal or from surrounding tissue to a yellowish hue.

Distended with gas - Expansion or enlargement from internal pressure of a gaseous substance, as in the lumen of an organ, usually making the walls stretched or thinned.

Distended with urine - Expansion or enlargement due to internal pressure of urine, usually in the urinary bladder and usually making the walls stretched or thinned.

Diverticulum - A pouch or sacculation of variable size created by herniation of the lining mucous membrane through a defect in the muscular coat of a tubular organ.

Edema - Excessive accumulation of tissue fluid is present in intercellular tissue spaces.

Edema, papilla – Excessive accumulation of tissue fluid within the interstitium of the papilla which results in rarification or myxomatous appearance of the papilla and may also manifest as polypoid protrusions from the lateral surface of the papilla.

Endocarditis, valvular vegetative - A fibrin thrombus containing inflammatory cells and usually bacteria is on the valve surface.

Enlarged - The entire organ or tissue is bigger than normal size.

Erosion/ulcer - Necrosis and loss of the superficial architecture of the epithelium is an erosion. If the basement membrane is disrupted, the lesion is an ulcer.

Erosion/ulcer, limiting ridge - Occurring at the junction of the glandular and nonglandular regions of the stomach, necrosis and loss of architecture of the epithelium constitutes an erosion. If the basement membrane is disrupted the lesion is an ulcer.

Erythrocytosis/erythrophagocytosis, sinus - Some erythrocytes are in the sinuses or have been phagocytosed by macrophages in the sinuses. Erythrocytes in sinuses arrive via lymph from sites of hemorrhage elsewhere.

Exudate, luminal - Material, such as fluid, cells and/or cellular debris, which has escaped from blood vessels and has been deposited within the lumen of a hollow organ or tissue.

PATHOLOGY GLOSSARY

Exudate, nasal passage - The nasal passages contain inflammatory cells, mucus, and/or desquamated nasal cells or erythrocytes.

Fibroadenoma - A benign neoplasm of the mammary gland consisting of neoplastic proliferation of ductular and/or alveolar epithelium and fibrous connective tissue.

Fibroma - A benign neoplasm composed mainly of fibrous or fully developed connective tissue.

Fibrosarcoma - A malignant neoplasm derived from fibroblasts that produce collagen.

Fibrosis - The proliferation of fibroblasts and the production of collagen resulting in the formation of fibrous connective tissue.

Fibrosis, capsular - An increased thickness of the capsule of an organ due to the proliferation of fibroblasts and increased collagen production.

Fibrous osteodystrophy - A lesion involving cortical or trabecular bone and generally characterized by an increase in osteoclasts in Howship's lacunae, atrophy of trabeculae, and proliferation of fibrous connective tissue in the marrow spaces.

Fluid, clear - The presence of liquid that is clear.

Fluid, red - The presence of liquid of a reddish color.

Fluid, white - The presence of liquid of a whitish color.

Focus/foci, black - One or more discrete areas exhibiting a black coloration, which is/are different from the color of the surrounding tissue.

Focus/foci, brown - One or more discrete areas exhibiting a brownish coloration, which is/are different from the color of the surrounding tissue.

Focus/foci, red - One or more discrete areas exhibiting a reddish coloration, which is/are different from the color of the surrounding tissue.

Focus/foci, tan - One or more discrete areas exhibiting a yellowish-brown coloration, which is/are different from the color of the surrounding tissue.

Focus/foci, white - One or more discrete areas exhibiting a very light or pale coloration, which is/are different from the color of the surrounding tissue.

Focus/foci, yellow - One or more discrete areas exhibiting a yellowish coloration, which is/are different from the color of the surrounding tissue.

PATHOLOGY GLOSSARY

Focus of cellular alteration, basophilic - Localized liver lesions recognized by increased basophilic tinctorial staining of hepatocytes compared to adjacent hepatic parenchyma. Foci usually range in size from less than a single hepatic lobule up to multiple lobules in greatest dimension. Cells are often smaller than hepatocytes in adjacent normal parenchyma, but may be enlarged. Portal triads and central veins are present in larger foci. Hepatocytes in these foci may merge imperceptibly with adjacent parenchyma or may be sharply demarcated. Very large lesions or those with hypertrophied cells may distort or compress surrounding hepatic plates around a small portion of the periphery. There is little to no disruption of hepatic lobular architecture. Cells from basophilic foci sometimes encroach on veins, but do not show evidence of local or distant metastasis. Foci of cellular alteration are believed to represent a reversible focal metabolic alteration of a group of hepatocytes. Some foci, under the influence of certain environmental conditions, may progress to neoplasia.

Focus of cellular alteration, clear - Localized liver lesions recognized by a clear cytoplasmic space or poorly staining cytoplasm compared to adjacent hepatic parenchyma. The cytoplasm of cells from clear cell foci have been shown to contain abundant glycogen. Foci usually range in size from less than a single hepatic lobule up to multiple lobules in greatest dimension. Cells are often minimally to markedly larger than hepatocytes in adjacent normal parenchyma. Portal triads and central veins are present in larger foci. Hepatocytes in these foci may merge imperceptibly with adjacent parenchyma or may be sharply demarcated. Very large lesions or those with hypertrophied cells may distort or compress surrounding hepatic plates around a small potion of the periphery. There is little to no disruption of hepatic lobular architecture. Foci of cellular alteration are believed to represent reversible focal metabolic alteration of a group of hepatocytes. Some foci, under the influence of certain environmental conditions, may progress to neoplasia.

PATHOLOGY GLOSSARY

Focus of cellular alteration, eosinophilic - Localized liver lesions recognized by densely eosinophilic or faintly granular pink staining of hepatocytes compared to adjacent hepatic parenchyma. Cells from eosinophilic foci have been shown to contain excess glycogen and smooth endoplasmic reticulum. Foci usually range in size from less than a single hepatic lobule up to multiple lobules in greatest dimension. Cells are often larger than hepatocytes in adjacent normal parenchyma. Portal triads and central veins are present in larger foci. Hepatocytes in these foci may merge imperceptibly with adjacent parenchyma or may be sharply demarcated. Very large lesions or those with hypertrophied cells may distort or compress surrounding hepatic plates around a small potion of the periphery. There is little to no disruption of hepatic lobular architecture. Foci of cellular alteration are believed to represent reversible focal metabolic alteration of a group of hepatocytes. Some foci, under the influence of certain environmental conditions, may progress to neoplasia.

Fold/rosette, retinal - There is focal juxtaposition of photoreceptor outer segments and lack of contact with the pigment epithelium.

Foreign material - Any material not made by the cells or tissues and which is not usually found in the location in question.

Fracture - A break or rupture, especially in a bone.

Fracture/callus - There is discontinuity of cortical bone. Depending on the amount of time elapsed since the bone was broken, there may be a proliferative repair response ranging from mesenchymal hyperplasia, differentiation into the cartilage model, or conversion of the cartilage model into bone.

Fungus/yeast - The presence of fungus and or yeast within a tissue.

Galactocele - Dilated ducts and/or alveoli in mammary tissue containing secretory material, cellular debris, and sometimes inflammatory cells.

Ganglioneuroma, benign - A benign neoplasm composed of nerve fibers and mature ganglion cells.

Granular cell tumor, benign - A benign neoplasm composed of polygonal cells with abundant pink granular cytoplasm. The neoplasm can arise in various organs and its cell of origin has not been conclusively determined.

Granuloma - A well circumscribed focus of granulomatous inflammation in which macrophages predominate, with or without multinucleated giant cells, and lymphocytes, plasma cells, and fibroblasts. Fibrous connective tissue may form the peripheral zone.

PATHOLOGY GLOSSARY

Granuloma, foreign body - A long-standing inflammatory reaction of a tissue to an irritant in which macrophages predominate, with lymphocytes, plasma cells and fibroblasts also present with or without multinucleated giant cells. The given foreign body is often incorporated in the tissue reaction.

Granuloma, spermatic - A long-standing reaction in response to ectopic spermatozoa in the testis or epididymis. There are associated areas of granulomatous inflammation, usually with a foreign body reaction, which form around the escaped spermatozoa.

Hair sparse - A natural or abnormal deficiency of hair.

Hemangioma - A benign vascular neoplasm formed by proliferation of endothelial cells forming well-defined vascular spaces.

Hemangiosarcoma - A malignant neoplasm formed by proliferation of endothelial cells forming vascular spaces.

Hematopoiesis, extramedullary - The formation and development of blood cells outside the bone marrow.

Hematopoiesis, extramedullary, increased - The increased formation and development of blood cells outside the bone marrow in areas where hematopoiesis is commonly observed.

Hemorrhage - The presence of blood outside the vascular system.

Histiocytosis, alveolar - Increased numbers of alveolar macrophages with abundant foamy cytoplasm in alveolar spaces. These are often subpleural (ie: foam cell foci) and in more peripheral lung regions.

Histiocytosis, sinus - The presence of macrophages or histiocytes with abundant foamy cytoplasm within the network of branching and anastomosing channels between the medullary cords of lymph nodes.

Hyaline, droplets, increased - Proximal renal tubular cells contain increased numbers of round hyaline to refractile bodies in the cytoplasm.

Hydronephrosis, bilateral - Both kidneys have a dilated pelvis. Early in the course of disease, minimal dilatation of the pelvis and slight compression of adjacent parenchyma are present. With time as severity increases, the pelvis dilates so extensively as to compress and destroy most renal parenchyma.

Hydronephrosis, unilateral - One kidney has a dilated pelvis. Early in the course of disease, minimal dilatation of the pelvis and slight compression of adjacent parenchyma are present. With time as severity increases, the pelvis dilates so extensively as to compress and destroy most renal parenchyma.

Hyperkeratosis - Excessive thickening of the keratin layer of a keratinized, stratified squamous epithelium-covered surface.

PATHOLOGY GLOSSARY

Hyperostosis - An excessive increase in the amount of bone, similar to exostosis, but without associated cartilage proliferation.

Hyperplasia - A non-neoplastic proliferation of normal cells in a tissue.

Hyperplasia, acinar cell, focal - A circumscribed spherical or oval lesion in the pancreas composed of well-differentiated acinar cells arranged in a prominent tubular glandular pattern resulting from enlargement and elongation of constituent acini. There may be some compression of the adjacent tissue.

Hyperplasia, bile duct - A non-neoplastic proliferation or increase in the number of small bile ducts, lined by normal-appearing epithelium, resulting in the presence of aggregations of bile ducts in the portal areas of the liver lobule. Bile duct hyperplasia is often associated with a degree of periportal fibrosis.

Hyperplasia, bronchiolar-alveolar - Poorly circumscribed areas in the alveolar portions of lung, lined with cuboidal epithelium. The affected foci may also have increased numbers of intraluminal alveolar cells and/or alveolar macrophages. Synonymous terms include Type II pneumocyte hyperplasia, alveolar epithelium hyperplasia, and septal cell hyperplasia.

Hyperplasia, C-cell, focal - A focal non-neoplastic proliferation of C-cells within the thyroid gland.

Hyperplasia, cervical fibromuscular - An increase in the amount of fibrous stroma and/or smooth muscle present in the cervix.

Hyperplasia, craniopharyngeal - A non-neoplastic proliferation arising from remnants of Rathke's pouch consisting of tubular structures and fusiform spindle cells. Most commonly seen in the pars nervosa and pars intermedia.

Hyperplasia, cystic endometrial - Endometrial glands may be increased in size and number. With time, glands become markedly dilated and the mucosa contains numerous multiloculated cysts.

Hyperplasia, diffuse - A non-neoplastic proliferation of the normal cells of an organ or tissue that is present throughout the entire organ or tissue.

Hyperplasia, diffuse, pars distalis - A diffuse increase in similar appearing endocrine cells that blends with and does not compress adjacent pituitary tissue.

Hyperplasia, endometrial - Proliferative change of the uterus, characterized by papillary projections of the endometrium into the lumen without an increase of epithelial cell size.

Hyperplasia, epidermal - An increase in the number of epithelial cells comprising the epidermis.

Hyperplasia, epithelial cell - A non-neoplastic proliferation of the epithelial cell components of a tissue or organ.

PATHOLOGY GLOSSARY

Hyperplasia, epithelial, limiting ridge - A non-neoplastic proliferation of the epithelial cell components of the limiting ridge separating the glandular and non-glandular portions of the stomach.

Hyperplasia, epithelial, nonglandular - A non-neoplastic proliferation of the epithelial cell components of a nonglandular tissue, most commonly used in the stomach.

Hyperplasia, fibromuscular - An increase in the amount of fibrous stroma and/or smooth muscle in the wall of the cervix or the uterus.

Hyperplasia, focal - A focal increase in number of cells, which may vary slightly in size or tinctorial features compared to adjacent parenchymal cells.

Hyperplasia, focal cortical - A focal area of the cortex consists of cortical cells with increased cytoplasmic volume.

Hyperplasia, focal medullary - Small to medium-sized aggregates of basophilic cells are present around the periphery of the medulla. Compression of adjacent cortex is absent or minimal.

Hyperplasia, focal, pars distalis - A focal increase in similar appearing endocrine cells that blends with and does not compress adjacent pituitary tissue.

Hyperplasia, follicular cell - A non-neoplastic proliferation of thyroid follicular cells.

Hyperplasia, granulocytic - An increase in the number of granulocyte precursor cells and granulocytes present.

Hyperplasia, hepatocellular regenerative - There is an increase in the number of hepatocytes, generally forming nodular areas, separated by areas of necrosis, inflammation, and/or fibrosis of the liver.

Hyperplasia, interstitial cell - A non-neoplastic proliferation of specific cellular components of the ovary or of the aggregates of interstitial cells between the seminiferous tubules of the testis.

Hyperplasia, islet cell - A non-neoplastic proliferation of cells populating the Islets of Langerhans of the pancreas.

Hyperplasia, lobular - A non-neoplastic proliferation of the cellular elements of a particular lobule of a multilobular tissue or organ.

Hyperplasia, lymphocyte/plasmacyte medulla - An increase in the number of lymphocytes and/or plasmacytes in the medulla.

Hyperplasia, lymphoid, generalized - A non-neoplastic increase in the number or density of lymphocytes within all lymphoid compartments of an organ.

Hyperplasia, lymphoid, medulla - A non-neoplastic increase in the number or density of lymphocytes within the medullary region of the thymus or a lymph node.

PATHOLOGY GLOSSARY

Hyperplasia, mixed - An increase in cells of both the erythrocytic and granulocytic series.

Hyperplasia, mucosal - A non-neoplastic proliferation of the epithelial cells comprising the mucosa. Glandular differentiation may be unchanged, increased, or absent. Mitotic figures may be increased and extension of epithelial cells into the submucosa may be present.

Hyperplasia, papillary/nodular transitional cell - An increase in number of transitional cells forming nodules or finger-like projections. In the more severe (grades 3 or 4) hyperplasias, elongated epithelial cords or nests may extend deep into the underlying lamina and even through the muscle wall.

Hyperplasia, reactive red pulp/stromal - Hypercellularity of splenic red pulp characterized by mixed cell accumulation/proliferation of reticuloendothelial cells, macrophages, neutrophils, and hematopoietic cells. The reaction is typical of chronic inflammation, systemic antigenemia, septicemia, and immunologic inflammatory conditions.

Hyperplasia, sex-cord/stromal - A non-neoplastic proliferation of the sex-cord/stromal cells of the ovary.

Hyperplasia, simple transitional cell - An increase in transitional cells in the mucosa.

Hyperplasia, squamous cell - An increase in the number of lining epithelial cells covering a mucosal or dermal surface.

Hyperplasia, squamous epithelium - An increase in the number of squamous cells lining a squamous-covered mucosa or dermis.

Hyperplasia, transitional cell - The transitional cell layer is focally or diffusely thickened by an increase in the number of cells present.

Hyperplasia, tubular - A non-neoplastic proliferation of tubules or the cells lining the tubules of an organ.

Hyperplasia, type II cell - Some alveoli are lined by cuboidal type II cells.

Hypertrophy, focal cortical - A cluster of cortical cells are enlarged, compression is not present.

Hypertrophy, hepatocyte, centrilobular - Hepatocytes around central veins are enlarged.

Hypertrophy, hepatocyte, panlobular - Hepatocytes throughout the lobule are enlarged.

Hypertrophy/hyperplasia, bronchiolar/bronchial - An increase in the size (hypertrophy) or number (hyperplasia) of respiratory epithelial cells lining bronchioles and bronchi.

PATHOLOGY GLOSSARY

Hypertrophy/hyperplasia, follicular cell - An increase in the size and/or numbers of follicular cells.

Hypertrophy/hyperplasia, goblet cell - An increase in size and/or number of goblet cells.

Impacted - Wedged or packed in, so as to fill or block an organ or a passage.

Infarct - A prominent area of discrete necrosis caused by interruption of normal blood supply.

Infiltration/inflammation, mixed cell - The presence of mixed inflammatory cells (e.g. neutrophils, macrophages, lymphocytes, and plasma cells) and/or hematopoietic cells.

Infiltration, lymphoid, perivascular - An increased number of lymphocytes within the tunica adventitia and/or adjacent connective tissue of blood and/or lymph vessels.

Infiltration, mononuclear cell - Increased numbers of cells with nonsegmented nuclei, particularly lymphocytes, plasma cells and/or histiocytes (macrophages), within an organ or tissue.

Inflammation - A tissue reaction consisting of varying degrees of leukocytic infiltration with or without vascular dilation, protein exudation, and edema.

Inflammation, acute - A tissue reaction typically seen early in the inflammatory process characterized by neutrophils and/or fibrin.

Inflammation, chronic-active - An inflammatory reaction with both a chronic and an acute component; consisting of neutrophils, lymphocytes, plasma cells, macrophages, fibroblasts, and collagenous connective tissue.

Inflammation, embolic - Inflammation is associated with hematogenous spread from a source elsewhere. Bacteria are usually implicated.

Inflammation, granulomatous - An inflammation reaction characterized by a predominance of regular to epithelioid macrophages with or without multinucleated giant cells and connective tissue.

Inflammation, hair follicle/epidermis - A mixed inflammatory cell infiltrate present in hair follicles and/or in the epidermis.

Inflammation, peritoneal - Leukocytic infiltration of the peritoneum, the thin serous membrane covering the abdominal wall and abdominal organs.

Inflammation, perivascular - Accumulation of inflammatory cells around vessels.

Inflammation, subacute/chronic - Infiltration of a tissue by lymphocytes, monocytes, and/or macrophages; an occasional neutrophil, plasma cell, or giant cell may also be present and some fibrous connective tissue may have been deposited.

PATHOLOGY GLOSSARY

Intussusception - The telescoping of one part of a tubular organ into the lumen of an immediately adjoining part.

Irregular surface - A tissue or organ with an external aspect or surface that is irregular.

Keratoacanthoma - A benign epithelial neoplasm of the hair follicles of the skin which is crateriform or invaginated into the dermis and subcutis. It consists of an irregular and nodular squamoous epithelial wall surrounding a central cystic space filled with keratin.

Laceration/perforation - A cut, tear, rupture, or pierced hole.

Leiomyoma - A benign neoplasm derived from smooth muscle.

Leiomyosarcoma - A malignant neoplasm of smooth muscle origin.

Leukemia, granulocytic - A neoplastic condition arising in the bone marrow involving hematopoietic cells of granulocytic lineage.

Leukemia, large granular lymphocyte - Also referred to as large granular lymphocyte lymphoma, this is a neoplastic condition involving large granular lymphocytes which usually originates in the marginal zone of the spleen and spreads to the blood and other organs.

Leukocytosis, sinusoidal - Increased numbers of white blood cells within the lumens of sinusoids.

Leukocytosis, vascular - An increase in the number of white blood cells within the vasculature of organs or tissues.

Lipoma - A benign neoplasm composed of mature fat cells.

Luteoma - A benign ovarian neoplasm of sex cord-stromal cells in which there has been luteinization of the cells.

Lymphangiectasis - Dilatation of the lymphatic vessels or spaces (sinusoids).

Lymphoma - A malignant neoplasm of lymphocytic origin.

Macrophages, alveolar - Large mononuclear cells with abundant cytoplasm present within the alveoli of the lung.

Macrophages, pigmented - Presence of macrophages containing pigmented material within the cytoplasm.

Macrophages, pigmented alveolar - The cytoplasm of alveolar macrophages contains pigment.

Mass - A focal abnormal enlargement in an organ or tissue.

Melanoma, amelanotic - A neoplasm comprised of melanocytes that do not contain melanin pigment.

Mesothelioma, malignant - A malignant neoplasm of mesothelial cells, the layer of flat cells which line the coelom or body cavities.

PATHOLOGY GLOSSARY

Metaplasia, osseous - Formation of bone in an extraskeletal site through a non-neoplastic transformation of normal adult tissue.

Metaplasia, squamous - A non-neoplastic alteration in non-squamous epithelial cells to squamous epithelial cells.

Mineralization - The formation or deposition of mineral in an organ or tissue.

Mineralization, focal - There is focal mineralization present.

Mineralization, myofiber - The presence of mineral deposits within the muscle cells of the heart.

Mineralization, pelvic - The presence of mineral deposits in the pelvis of the kidney.

Mineralization, tubular - The presence of mineral deposits within tubules.

Mineralization, vascular - The presence of mineral deposits within the tunica intima, tunica media and/or tunica adventitia of blood vessels.

Mucus increased – An increase in the amount of mucus in an organ that secretes mucus or an organ into which mucus can drain such as lung.

Multinucleated, hepatocytes - Occasional hepatocytes contain two or more nuclei.

Necrosis - Death of tissue in a living animal.

Necrosis, fat - Death of adipose tissue in a living animal in which the neutral fats in the cells of adipose tissue are split into fatty acids and glycerol.

Necrosis, focal - A focal area of dead tissue in a living animal.

Necrosis, hepatocytes, centrilobular - Dead hepatocytes are present mainly around central veins.

Necrosis, individual hepatocyte - Individual hepatocytes are dead.

Necrosis, papillary - Death of tissue in a living animal, usually as individual cells, groups of cells, or in localized areas of the papilla.

Neovascularization, corneal - Usually a sequela to inflammation, small caliber blood vessels are present in the stroma of the cornea.

Nephropathy, chronic progressive - A spontaneous progressive renal disease of laboratory rodents, characterized by the presence of glomerular, tubular, and interstitial degenerative and inflammatory changes, including glomerular distention, glomerulosclerosis, thickened basement membranes, tubular basophilia, tubular casts, interstitial fibrosis, and subacute to chronic inflammation.

Nodule - A small lump, swelling or collection of tissue.

Odontitis/periodontitis - Inflammation of the tooth and/or the tissue around the tooth.

PATHOLOGY GLOSSARY

Odontodysplasia - The tissues comprising the tooth have formed abnormally and are present in an improper orientation or amount.

Oligospermia/germ cell debris, bilateral - The lumen contents of both epididymides have fewer spermatozoa than normal and contain abnormal germ cells and/or cytoplasmic or nuclear debris.

Oligospermia/germ cell debris, unilateral - The lumen contents of one epididymis have fewer spermatozoa than normal and contain abnormal germ cells and/or cytoplasmic or nuclear debris.

Osteoarthritis/pododermitis - Degenerative joint disease generally characterized by inflammation of the bone and/or cartilage, degeneration of the articular cartilage, hypertrophy of bone at the margins of the lesions and/or changes in the synovial membrane (osteoarthritis) or a chronic inflammatory lesion of the foot (pododermatitis).

Osteosarcoma - A malignant neoplasm of bone.

Papilloma, squamous cell - A branching or lobulated benign neoplasm composed of proliferating squamous epithelial cells.

Pheochromocytoma, benign - A benign neoplasm arising from chromaffin cells of the adrenal medulla or sympathetic paraganglia.

Pheochromocytoma, malignant - A malignant neoplasm arising from chromaffin cells of the adrenal medulla or sympathetic paraganglia.

Phthisis bulbi - A shrunken, non-functioning globe of the eye due to severe ocular disease and/or injury.

Pneumonitis, uremic - Mineralization of alveolar septae and blood vessels with accumulations of alveolar macrophages in mineralized areas secondary to chronic progressive nephropathy and/or parathyroid gland hyperplasia.

Polyarteritis - One or more arteries has inflammation ranging from acute to chronic, usually chronic.

Polyp, glandular - A benign outgrowth protruding from a mucous membrane consisting primarily of glandular components.

Polyp, stromal - A benign outgrowth protruding from a mucous membrane consisting primarily of stromal components.

Prolapse - The protrusion of a portion of an organ through a body opening.

Proliferation, fibro-osseous - A proliferation of bone and fibrous connective tissue.

Pyelitis - Inflammation of the pelvis of the kidney.

Pyelonephritis, bilateral - Inflammation in the pelvis and renal parenchyma affecting both kidneys.

Sarcoma, histiocytic - A malignant tumor of the reticular system composed predominantly of neoplastic histiocytes.

PATHOLOGY GLOSSARY

Sarcoma, stromal - A malignant mesenchymal neoplasm that arises from the endometrial stroma of the uterus.

Schwannoma, benign - A benign neoplasm arising from the Schwann cell of the peripheral nervous system.

Schwannoma, malignant - A malignant neoplasm arising from the Schwann cell of the peripheral nervous system.

Small - Comparatively little in size or dimension; not as large as normally expected.

Swollen/thickened - Generally, an enlargement of a non-discrete tissue.

Synechia - Adhesion of parts, especially adhesion of the iris to the cornea or to the lens.

Thrombus - A plug or clot formed inside a blood vessel or heart chamber by coagulation of the blood in a living animal.

Thymoma, malignant - A malignant neoplasm of the epithelial elements of the thymus.

Ulcer, plantar/palmar - An ulcer located on the contact surface of the palmar or ventral surface of the forelimb (below the carpus) or the plantar or ventral surface of the hindlimb (below the tarsus).

Vacuolation, centrilobular - The presence of prominent cytoplasmic vacuoles primarily in hepatocytes surrounding the central vein of hepatic lobules.

Vacuolation, diffuse - The presence of cytoplasmic vacuoles throughout an organ or tissue.

Vacuolation, focal - The formation of prominent vacuoles within a focal area of a tissue or organ.

Vacuolation, median cleft - In the liver, a focal area of cytoplasmic hepatocellular vacuolation in the area of the attachment of the falciform ligament; thought to be caused by tension of the ligament on the liver (tension lipidosis).

Vacuolation, midzonal - The presence of cytoplasmic vacuoles in hepatocytes in the midzonal regions of the lobule.

Vacuolation, periportal - The presence of cytoplasmic vacuoles primarily in hepatocytes surrounding the portal triads of hepatic lobules.

Within normal limits - Tissue considered to be normal under the conditions of the study and considering the age, sex, and strain of the animal concerned. Alterations may be present which, under other circumstances, would be considered deviations from normal.

Appendix A
Tissues and Organs Collected, Weighed, and Examined

The following list constitutes the full complement of organs and tissues:

- Adrenal (2)*
- Aorta
- Bone with marrow [femur]
- Bone with marrow [sternum]
- Bone marrow smear [2 collected][a]
- Brain [cerebrum, midbrain, cerebellum, medulla/pons]*
- Coagulating gland (2)
- Epididymis (2)*
- Eye including retina and optic nerve (2)
- GALT [Gut Associated Lymphoid Tissue]
- Gastrointestinal tract:
  esophagus
  stomach [glandular and nonglandular]
  duodenum
  jejunum
  ileum
  cecum
  colon
  rectum
- Gonads:
  ovary (2)* with oviduct (2)*
  testis (2)*
- Gross lesions
- Harderian gland (2)
- Heart*
- Joint, tibiofemoral
- Kidney (2)*
- Lacrimal gland, exorbital (2)
- Larynx
- Liver [3 sections collected; 2 examined]*
- Lung with bronchi [collected whole; 2 sections examined]
- Lymph nodes: mandibular [2 collected; 1 examined], mesenteric, and regional where applicable
- Mammary gland [process females only]
- Nose [Levels A, B, C, and D]
- Pancreas
- Pharynx
- Pituitary
- Prostate and seminal vesicle (2)
- Salivary gland, mandibular/sublingual [2 collected; 1 examined]
- Salivary gland, parotid [2 collected; 1 examined]
- Sciatic nerve
- Skeletal muscle, biceps femoris
- Skin
- Spinal cord [cervical, thoracic, and lumbar]
- Spleen*
- Thymus
- Thyroid/parathyroid (2)*
- Tissue masses
- Tongue
- Trachea
- Ureter (2)
- Urinary bladder
- Uterus [both horns]/Cervix*
- Vagina

[a]Bone marrow smears were collected at necropsy and held.

(2) Paired organ
*Weighed organ

Appendix B
Pathology Tables

Table 1
Incidence of Probable Cause of Death/Moribundity

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Incidence of Probable Cause of Death/Moribundity - MALE

Cause of Death	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
Number of Animals	70	70	70	70
Summary of Animal Disposition				
died after blood collection	0	1	0	2
died after dosing	0	0	1	0
died prior to euthanasia	0	0	1	0
euthanized *in extremis*	31	29	24	24
found dead	24	20	26	26
terminal necropsy	15	20	18	18
Cause of Death				
accidental injury	0	1	0	3
accidental, died after bleeding	0	0	0	1
adrenal gland angiectasis/cystic degeneration/necrosis	1	0	0	0
aspiration of foreign material	0	1	0	0
bone tumor	1	0	0	0
brain hemorrhage/necrosis	0	0	0	1
brain tumor	0	3	1	0
chronic progressive nephropathy/uremia	3	0	2	0
dosing injury	2	4	5	3
fibrosarcoma/fibroma	1	2	3	3
foot/feet inflammation	0	2	1	0
gastrointestinal tumor	0	2	0	0

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Incidence of Probable Cause of Death/Moribundity - MALE

Cause of Death	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
Number of Animals	70	70	70	70
Cause of Death				
heart failure/atrial thrombus	0	0	0	1
heart inflammation/necrosis	0	0	1	1
hemangiosarcoma/hemangioma	0	1	0	0
hind limb/leg inflammation	0	1	0	0
histiocytic sarcoma	1	0	1	3
inflammation/septicemia	0	1	0	0
kidney tumor	0	1	0	1
larynx/pharynx tumor	0	0	0	1
leukemia	1	0	1	0
lipoma/liposarcoma	0	2	0	1
liver inflammation/necrosis	0	2	0	0
liver tumor	1	0	0	0
lung thrombus	1	0	0	0
lymphoid tumor	0	0	1	0
mammary tumor	1	0	0	1
nerve, sciatic degeneration, axonal/myelin	1	0	0	0
nose/oral inflammation/ulceration	5	0	2	1
osteoarthritis/pododermatitis	4	2	0	1
pituitary tumor	19	13	14	14
probable dosing injury	0	1	2	0
schwannoma	0	0	0	1
skin inflammation/necrosis	1	0	0	0
skin tumor	0	1	2	0

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Incidence of Probable Cause of Death/Moribundity - MALE

Cause of Death	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
Number of Animals	70	70	70	70
Cause of Death				
spinal cord tumor	1	1	0	1
tail erosion/ulcer	0	1	0	0
undetermined	8	7	11	11
urogenital inflammation/obstruction/calculi	3	1	5	3

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Incidence of Probable Cause of Death/Moribundity - FEMALE

Cause of Death	0 mg/kg/day	1 mg/kg/day	50 mg/kg/day	500 mg/kg/day
Number of Animals	70	70	70	70
Summary of Animal Disposition				
died after dosing	0	0	0	1
died prior to euthanasia	0	2	0	0
euthanized *in extremis*	41	32	45	32
found dead	13	14	10	19
terminal necropsy	16	22	15	18
Cause of Death				
aspiration of foreign material	0	1	0	0
bone tumor	0	0	1	0
clitoral gland tumor	0	1	0	0
dosing injury	1	0	1	4
fibrosarcoma/fibroma	2	1	1	1
heart failure/atrial thrombus	0	1	0	0
inflammation/septicemia	0	0	0	1
kidney inflammation/necrosis	0	0	0	7
kidneys fibrosis	0	0	0	1
liver tumor	0	0	0	1
loss of hindlimb function, cause undetermined.	1	0	0	0
lymphoid tumor	0	0	2	0
mammary tumor	15	12	18	17
nose/oral tumor	0	0	0	1

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Incidence of Probable Cause of Death/Moribundity - FEMALE

Cause of Death	0 mg/kg/day	1 mg/kg/day	50 mg/kg/day	500 mg/kg/day
Number of Animals	70	70	70	70
Cause of Death				
pituitary tumor	26	27	30	17
probable dosing injury	1	0	0	0
schwannoma	0	1	1	0
skin inflammation/necrosis	1	0	0	0
skin tumor	0	0	1	0
thymus tumor	1	0	0	0
undetermined	4	3	0	0
uterus tumor	0	1	0	2
vagina prolapse	1	0	0	0
zymbals gland tumor	1	0	0	0

Table 2
Incidences of Gross Observations

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Incidences of Gross Observations - MALE
Interim

Tissue / Observation	Severity	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
Number of Animals Examined		10	10	10	10
all tissues					
within normal limits		7	5	8	7
cavity, abdominal					
mass	- present	0	1	0	0
eyes					
small	- moderate	0	1	0	0
eyes, retina					
small	- moderate	0	1	0	0
harderian glands					
enlarged	- mild	0	1	0	0
liver					
focus/foci, red	- mild	0	0	1	0
focus/foci, tan	- mild	0	0	0	1
pituitary gland					
enlarged	- moderate	1	0	0	0

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Incidences of Gross Observations - MALE
Interim

Tissue / Observation	Severity	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
Number of Animals Examined		10	10	10	10
seminal vesicles					
enlarged	- mild	0	1	0	0
skin					
hair sparse		1	1	0	0
	- mild	0	1	0	0
	- moderate	1	0	0	0
nodule	- present	0	1	0	0
spleen					
irregular surface	- mild	1	0	0	0
stomach, glandular					
swollen/thickened	- mild	0	0	0	1
testes					
enlarged	- mild	0	0	0	1
focus/foci, yellow	- mild	0	0	0	1
thyroid gland					
enlarged	- moderate	0	0	1	0

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Incidences of Gross Observations - FEMALE
Interim

Tissue / Observation	Severity	0 mg/kg/day	1 mg/kg/day	50 mg/kg/day	500 mg/kg/day
Number of Animals Examined		10	10	10	10
all tissues					
within normal limits		7	4	4	4
adipose tissue					
focus/foci, yellow	- mild	0	0	1	0
kidneys					
irregular surface	- minimal	0	0	0	1
liver					
focus/foci, red	- mild	0	0	1	0
lung with bronchi					
focus/foci, white	- mild	0	1	0	0
lymph node, axillary					
not identified	- no grade	0	0	1	0
lymph node, inguinal					
enlarged	- moderate	0	1	0	0

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Incidences of Gross Observations - FEMALE
Interim

Tissue / Observation	Severity	0 mg/kg/day	1 mg/kg/day	50 mg/kg/day	500 mg/kg/day
Number of Animals Examined		10	10	10	10
mammary gland					
swollen/thickened	- mild	0	1	0	0
ovaries					
cyst	- mild	0	0	1	0
pituitary gland					
enlarged		2	6	4	2
	- minimal	0	2	1	0
	- mild	2	2	2	1
	- moderate	0	2	0	0
	- severe	0	0	1	1
skin					
abrasion/scab	- mild	0	0	1	0
hair sparse		1	2	2	2
	- minimal	0	0	1	0
	- mild	0	2	1	2
	- moderate	1	0	0	0
skin, subcutis					
mass	- present	0	1	3	2

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Incidences of Gross Observations - FEMALE
Interim

Tissue / Observation	Severity	0 mg/kg/day	1 mg/kg/day	50 mg/kg/day	500 mg/kg/day
Number of Animals Examined		10	10	10	10
spleen					
small	- mild	0	0	1	0
thyroid gland					
absent	- no grade	0	0	1	0
uterus with cervix					
enlarged	- mild	0	0	0	1

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Incidences of Gross Observations - MALE
Terminal

Tissue / Observation	Severity	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
Number of Animals Examined		70	70	70	70
all tissues					
within normal limits		11	14	12	11
adipose tissue					
discoloration, yellow	- mild	0	0	0	1
focus/foci, red	- mild	0	0	1	0
focus/foci, yellow		1	1	0	0
	- minimal	0	1	0	0
	- mild	1	0	0	0
adrenal glands					
enlarged		2	3	1	3
	- mild	1	2	1	2
	- moderate	0	0	0	1
	- severe	1	1	0	0
mass	- present	0	1	0	1
not identified	- no grade	0	1	0	0
small	- moderate	0	1	0	1
animal/whole body					
body fat depleted	- moderate	1	0	1	1

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Incidences of Gross Observations - MALE
Terminal

Tissue / Observation	Severity	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
Number of Animals Examined		70	70	70	70
aorta					
discoloration, gray	- mild	0	0	1	0
bile duct, extrahepatic					
dilatation		1	0	1	0
	- mild	0	0	1	0
	- moderate	1	0	0	0
bone					
mass	- present	1	0	0	0
bone with bone marrow, femur					
mass	- present	1	0	0	0
bone, femur					
irregular surface	- moderate	0	1	0	0
cavity, abdominal					
adhesion	- mild	0	1	0	0
mass	- present	0	0	0	2
cavity, thoracic					
fluid, red	- mild	0	0	1	0
mass	- present	1	0	0	0

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Incidences of Gross Observations - MALE
Terminal

Tissue / Observation	Severity	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
Number of Animals Examined		70	70	70	70
coagulating glands					
small		1	0	0	1
	- mild	0	0	0	1
	- moderate	1	0	0	0
epididymides					
small	- mild	1	0	0	1
esophagus					
foreign material	- moderate	0	1	0	0
eyes					
absent/cannibalized	- no grade	4	2	4	1
cloudy		2	2	0	2
	- mild	1	0	0	2
	- moderate	1	2	0	0
discoloration, red	- moderate	0	1	0	0
discoloration, white	- mild	1	1	0	0
eyes, optic nerves					
absent/cannibalized	- no grade	1	1	3	0

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Incidences of Gross Observations - MALE
Terminal

Tissue / Observation	Severity	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
Number of Animals Examined		70	70	70	70
eyes, retina					
absent/cannibalized	- no grade	4	2	3	0
foot/feet					
abrasion/scab	- moderate	0	0	0	1
absent, portion	- no grade	0	1	0	0
enlarged		0	1	0	1
	- mild	0	1	0	0
	- moderate	0	0	0	1
fracture	- mild	0	0	0	1
swollen/thickened		3	2	1	2
	- mild	1	2	1	1
	- moderate	1	0	0	1
	- severe	1	0	0	0
ulcer, plantar/palmar		3	2	1	2
	- minimal	0	0	1	0
	- mild	1	0	0	2
	- moderate	1	1	0	0
	- severe	1	1	0	0
galt					
distended with gas	- moderate	0	0	0	1

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Incidences of Gross Observations - MALE
Terminal

Tissue / Observation	Severity	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
Number of Animals Examined		70	70	70	70
harderian glands					
absent, portion	- no grade	1	0	0	0
absent/cannibalized	- no grade	3	1	4	1
enlarged	- moderate	0	0	0	1
heart					
discoloration, white	- mild	0	0	1	0
focus/foci, red	- mild	0	0	1	0
hind limb/leg					
discoloration, red	- moderate	0	1	0	0
joint, tibiofemoral					
enlarged	- mild	0	1	0	0
kidneys					
cyst		2	5	1	0
	- mild	0	4	1	0
	- moderate	2	1	0	0
dilatation, pelvic	- mild	4	1	2	1
enlarged		1	2	1	3
	- mild	1	1	0	3
	- moderate	0	0	1	0
	- severe	0	1	0	0

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Incidences of Gross Observations - MALE
Terminal

Tissue / Observation	Severity	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
Number of Animals Examined		70	70	70	70
kidneys					
focus/foci, yellow	- mild	1	0	0	0
irregular surface		3	4	3	2
	- minimal	0	1	0	0
	- mild	0	3	1	1
	- moderate	3	0	2	1
mass	- present	0	1	0	0
nodule	- present	0	0	0	1
lacrimal glands, exorbital					
absent/cannibalized	- no grade	2	1	4	2
not identified	- no grade	0	1	1	0
small	- mild	0	1	0	0
large intestine, cecum					
distended with gas		0	0	0	2
	- mild	0	0	0	1
	- moderate	0	0	0	1
large intestine, colon					
distended with gas		0	0	0	2
	- mild	0	0	0	1
	- moderate	0	0	0	1

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Incidences of Gross Observations - MALE
Terminal

Tissue / Observation	Severity	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
Number of Animals Examined		70	70	70	70
larynx					
absent/cannibalized	- no grade	0	1	0	0
liver					
cyst	- mild	2	1	0	1
discoloration, tan		1	1	2	0
	- mild	1	0	0	0
	- moderate	0	1	2	0
enlarged		0	1	2	5
	- mild	0	1	2	4
	- moderate	0	0	0	1
focus/foci, red	- mild	0	0	0	1
focus/foci, tan		2	1	2	3
	- mild	2	1	2	2
	- moderate	0	0	0	1
focus/foci, yellow	- mild	1	0	0	0
mass	- present	2	2	1	3
lung with bronchi					
discoloration, red		1	0	1	0
	- mild	1	0	0	0
	- moderate	0	0	1	0
fluid, white	- mild	1	0	0	0

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Incidences of Gross Observations - MALE
Terminal

Tissue / Observation	Severity	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
Number of Animals Examined		70	70	70	70
lung with bronchi					
focus/foci, red		0	0	3	0
	- minimal	0	0	1	0
	- mild	0	0	2	0
focus/foci, tan	- mild	0	0	2	0
focus/foci, white	- mild	0	1	0	0
mass	- present	2	0	0	1
lymph node, axillary					
enlarged	- mild	1	0	0	1
not identified	- no grade	1	0	0	0
lymph node, generalized					
enlarged		1	0	1	0
	- mild	1	0	0	0
	- moderate	0	0	1	0
lymph node, hepatic					
enlarged	- moderate	1	1	1	0
not identified	- no grade	0	1	1	1

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H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Incidences of Gross Observations - MALE
Terminal

Tissue / Observation	Severity	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
Number of Animals Examined		70	70	70	70
lymph node, iliac					
enlarged		0	2	1	1
	- mild	0	1	0	1
	- moderate	0	1	1	0
lymph node, inguinal					
enlarged	- mild	0	1	0	0
not identified	- no grade	0	4	1	5
lymph node, mandibular					
absent/cannibalized	- no grade	2	1	0	1
discoloration, red	- mild	0	0	2	1
enlarged		1	1	2	0
	- mild	0	1	1	0
	- moderate	1	0	1	0
lymph node, mediastinal					
enlarged	- moderate	0	0	1	0
lymph node, mesenteric					
enlarged		1	2	2	0
	- mild	1	2	1	0
	- moderate	0	0	1	0

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Incidences of Gross Observations - MALE
Terminal

Tissue / Observation	Severity	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
Number of Animals Examined		70	70	70	70
lymph node, renal					
discoloration, red	- moderate	0	1	0	0
not identified	- no grade	0	0	0	1
mammary gland					
swollen/thickened	- mild	0	1	1	0
meninges					
swollen/thickened	- severe	0	0	0	1
mesentery/peritoneum					
abscess	- moderate	1	0	0	0
mass	- present	0	1	0	0
nodule	- present	0	1	0	0
nose					
focus/foci, white	- mild	1	0	0	0
pancreas					
edema	- mild	0	1	0	0
mass	- present	1	1	2	2
not identified	- no grade	0	0	0	1

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Incidences of Gross Observations - MALE
Terminal

Tissue / Observation	Severity	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
Number of Animals Examined		70	70	70	70
parathyroid glands					
enlarged		0	1	1	0
	- mild	0	1	0	0
	- severe	0	0	1	0
pharynx					
absent/cannibalized	- no grade	0	1	0	0
pituitary gland					
cyst		2	1	1	2
	- minimal	1	0	0	0
	- mild	1	1	1	1
	- severe	0	0	0	1
discoloration, red	- severe	1	0	0	0
enlarged		26	21	27	24
	- minimal	2	1	2	1
	- mild	4	4	4	6
	- moderate	7	3	6	7
	- severe	13	13	15	10
focus/foci, black	- mild	0	1	0	0
small	- moderate	0	0	1	0
prostate gland					
discoloration, tan	- moderate	0	0	1	0

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H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Incidences of Gross Observations - MALE
Terminal

Tissue / Observation	Severity	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
Number of Animals Examined		70	70	70	70
prostate gland					
edema	- moderate	1	0	0	0
enlarged		2	1	1	0
	- mild	1	1	0	0
	- moderate	1	0	1	0
focus/foci, yellow	- mild	0	1	0	0
mass	- present	0	0	1	0
salivary gland, mandibular					
absent/cannibalized	- no grade	1	1	0	1
salivary gland, parotid					
absent, portion	- no grade	1	0	0	0
absent/cannibalized	- no grade	1	1	0	1
salivary gland, sublingual					
absent/cannibalized	- no grade	1	1	0	1
seminal vesicles					
discoloration, green	- mild	1	0	0	0
enlarged		1	0	0	2
	- mild	0	0	0	2
	- moderate	1	0	0	0

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H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Incidences of Gross Observations - MALE
Terminal

Tissue / Observation	Severity	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
Number of Animals Examined		70	70	70	70
seminal vesicles					
small		3	1	2	3
	- mild	2	1	1	2
	- moderate	1	0	0	1
	- severe	0	0	1	0
skeletal muscle					
mass	- present	0	1	0	0
skin					
abrasion/scab		2	5	2	3
	- mild	2	3	2	2
	- moderate	0	2	0	1
absent portion/cannibalized	- no grade	0	1	0	0
hair sparse		1	1	0	0
	- mild	1	0	0	0
	- moderate	0	1	0	0
mass	- present	1	4	2	3
nodule	- present	1	2	2	1
swollen/thickened	- severe	0	0	1	0
skin, subcutis					
abscess	- mild	1	0	1	0
mass	- present	11	12	18	14

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H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Incidences of Gross Observations - MALE
Terminal

Tissue / Observation	Severity	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
Number of Animals Examined		70	70	70	70
skin, subcutis					
nodule	- present	0	0	1	1
small intestine, duodenum					
distended with gas	- moderate	0	0	0	1
small intestine, ileum					
distended with gas		1	0	0	2
	- mild	0	0	0	1
	- moderate	1	0	0	1
intussusception	- moderate	0	0	1	0
swollen/thickened	- moderate	0	1	0	0
small intestine, jejunum					
distended with gas	- moderate	1	0	0	1
enlarged	- moderate	0	1	0	0
impacted	- mild	0	1	0	0
mass	- present	0	2	0	0
spinal cord, cervical					
absent/cannibalized	- no grade	0	1	0	0
spleen					
cyst	- mild	1	0	0	0

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Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Incidences of Gross Observations - MALE
Terminal

Tissue / Observation	Severity	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
Number of Animals Examined		70	70	70	70
spleen					
discoloration, tan	- mild	0	1	0	0
enlarged		1	0	3	0
	- moderate	1	0	2	0
	- severe	0	0	1	0
focus/foci, tan	- mild	0	0	0	1
stomach					
distended with gas		1	0	0	1
	- mild	1	0	0	0
	- moderate	0	0	0	1
stomach, glandular					
focus/foci, brown	- mild	0	1	0	0
focus/foci, red	- mild	0	0	1	0
focus/foci, tan	- mild	0	1	0	1
irregular surface	- mild	0	1	1	0
swollen/thickened		0	0	3	1
	- mild	0	0	2	1
	- moderate	0	0	1	0
stomach, nonglandular					
focus/foci, brown	- mild	0	0	1	0

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Incidences of Gross Observations - MALE
Terminal

Tissue / Observation	Severity	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
Number of Animals Examined		70	70	70	70
stomach, nonglandular					
focus/foci, red		1	0	1	0
	- mild	0	0	1	0
	- moderate	1	0	0	0
focus/foci, tan		1	1	1	5
	- mild	1	1	1	4
	- moderate	0	0	0	1
focus/foci, yellow	- mild	1	0	0	0
irregular surface		1	3	2	1
	- mild	1	3	1	1
	- moderate	0	0	1	0
laceration/perforation	- moderate	0	1	0	0
mass	- present	1	0	0	0
nodule	- present	1	0	0	0
swollen/thickened	- mild	0	2	0	1
tail					
focus/foci, tan	- moderate	0	1	0	0
nodule	- present	1	0	0	0
testes					
discoloration, red	- moderate	0	0	0	1

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Incidences of Gross Observations - MALE
Terminal

Tissue / Observation	Severity	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
Number of Animals Examined		70	70	70	70
testes					
discoloration, tan		0	0	0	3
	- mild	0	0	0	2
	- moderate	0	0	0	1
enlarged		0	1	2	2
	- mild	0	0	2	1
	- moderate	0	1	0	1
focus/foci, red	- mild	0	0	1	0
focus/foci, tan		1	1	0	1
	- mild	0	1	0	1
	- moderate	1	0	0	0
small		5	3	4	3
	- mild	2	3	4	2
	- moderate	3	0	0	1
thymus					
cyst	- mild	0	1	0	0
enlarged	- moderate	0	0	1	0
mass	- present	1	0	0	1
nodule	- present	1	0	0	0
small	- severe	2	0	0	0

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H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Incidences of Gross Observations - MALE
Terminal

Tissue / Observation	Severity	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
Number of Animals Examined		70	70	70	70
thyroid gland					
enlarged		2	1	2	1
	- mild	1	0	1	1
	- moderate	1	1	0	0
	- severe	0	0	1	0
thyroid/parathyroid glands					
absent/cannibalized	- no grade	0	1	0	0
tongue					
absent portion/cannibalized	- no grade	1	2	2	1
absent/cannibalized	- no grade	0	2	1	1
tooth/teeth					
absent/broken/malocclusion/overgrown	- no grade	1	0	0	0
trachea					
absent/cannibalized	- no grade	0	1	0	0
fluid, white	- mild	1	0	0	0
ureters					
distended with urine		1	1	1	1
	- mild	1	1	1	0
	- moderate	0	0	0	1

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Incidences of Gross Observations - MALE
Terminal

Tissue / Observation	Severity	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
Number of Animals Examined		70	70	70	70
urinary bladder					
calculus/calculi		0	2	0	1
	- mild	0	0	0	1
	- moderate	0	2	0	0
cyst	- mild	0	1	0	0
distended with urine		3	1	6	3
	- mild	0	1	0	0
	- moderate	2	0	5	2
	- severe	1	0	1	1
irregular surface	- mild	0	0	1	0
swollen/thickened	- mild	0	0	0	1
zymbal`s gland					
focus/foci, white	- mild	0	0	0	1

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Incidences of Gross Observations - FEMALE
Terminal

Tissue / Observation	Severity	0 mg/kg/day	1 mg/kg/day	50 mg/kg/day	500 mg/kg/day
Number of Animals Examined		70	70	70	70
all tissues					
within normal limits		4	1	2	8
adipose tissue					
discoloration, red	- mild	0	1	0	0
discoloration, yellow	- mild	0	1	0	0
focus/foci, yellow	- mild	0	0	0	1
swollen/thickened	- mild	0	0	0	1
adrenal glands					
cyst		0	1	1	3
	- mild	0	1	0	2
	- moderate	0	0	1	1
enlarged		9	7	10	12
	- minimal	0	0	1	2
	- mild	7	6	8	8
	- moderate	2	1	1	2
focus/foci, red	- mild	0	0	1	0
irregular surface	- moderate	0	0	1	0
small	- mild	1	0	0	0

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Incidences of Gross Observations - FEMALE
Terminal

Tissue / Observation	Severity	0 mg/kg/day	1 mg/kg/day	50 mg/kg/day	500 mg/kg/day
Number of Animals Examined		70	70	70	70
animal/whole body					
body fat depleted		3	1	2	1
	- mild	2	0	1	1
	- moderate	1	1	1	0
bone, mandible					
mass	- present	1	0	0	0
brain					
discoloration, tan	- moderate	0	0	0	1
focus/foci, black	- mild	0	1	0	0
cavity, abdominal					
fluid, red	- mild	0	0	0	1
cavity, thoracic					
fluid, clear	- minimal	0	0	1	0
fluid, red		1	0	0	1
	- minimal	1	0	0	0
	- moderate	0	0	0	1
mass	- present	1	1	0	0
clitoral glands					
enlarged	- mild	0	0	0	1

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Incidences of Gross Observations - FEMALE
Terminal

Tissue / Observation	Severity	0 mg/kg/day	1 mg/kg/day	50 mg/kg/day	500 mg/kg/day
Number of Animals Examined		70	70	70	70
ears					
nodule	- present	1	0	1	0
eyes					
absent	- no grade	0	1	0	0
absent/cannibalized	- no grade	2	0	1	0
cloudy	- mild	0	0	0	1
eyes, optic nerves					
absent/cannibalized	- no grade	1	0	1	0
eyes, retina					
absent/cannibalized	- no grade	2	1	1	0
foot/feet					
absent portion/cannibalized	- no grade	0	0	0	1
ulcer, plantar/palmar	- mild	0	1	1	0
harderian glands					
absent/cannibalized	- no grade	1	0	0	0
discoloration, tan	- moderate	0	0	1	0

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Incidences of Gross Observations - FEMALE
Terminal

Tissue / Observation	Severity	0 mg/kg/day	1 mg/kg/day	50 mg/kg/day	500 mg/kg/day
Number of Animals Examined		70	70	70	70
kidneys					
cyst	- moderate	0	0	0	1
dilatation, pelvic	- mild	0	1	0	1
discoloration, tan		0	0	1	1
	- minimal	0	0	1	0
	- mild	0	0	0	1
enlarged	- mild	0	0	0	1
focus/foci, tan	- mild	1	0	0	1
focus/foci, white	- mild	0	0	0	1
irregular surface		0	0	0	16
	- minimal	0	0	0	1
	- mild	0	0	0	15
small	- moderate	0	0	0	1
lacrimal glands, exorbital					
absent/cannibalized	- no grade	1	1	1	0
small	- mild	0	0	0	1
large intestine, cecum					
focus/foci, red	- mild	0	1	0	0

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Incidences of Gross Observations - FEMALE
Terminal

Tissue / Observation	Severity	0 mg/kg/day	1 mg/kg/day	50 mg/kg/day	500 mg/kg/day
Number of Animals Examined		70	70	70	70
liver					
cyst		2	1	0	0
	- mild	1	0	0	0
	- moderate	1	1	0	0
discoloration, brown	- moderate	0	0	0	1
discoloration, tan		1	1	1	0
	- minimal	0	0	1	0
	- mild	1	1	0	0
enlarged	- moderate	0	0	0	1
focus/foci, red		2	0	3	0
	- minimal	0	0	1	0
	- mild	2	0	2	0
focus/foci, tan		1	1	1	8
	- mild	1	1	1	7
	- moderate	0	0	0	1
focus/foci, white	- moderate	0	0	0	1
mass	- present	0	0	0	12
nodule	- present	0	0	0	2
lung with bronchi					
discoloration, pink		0	0	1	1
	- mild	0	0	0	1
	- moderate	0	0	1	0
discoloration, red	- moderate	0	0	0	1

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Incidences of Gross Observations - FEMALE
Terminal

Tissue / Observation	Severity	0 mg/kg/day	1 mg/kg/day	50 mg/kg/day	500 mg/kg/day
Number of Animals Examined		70	70	70	70
lung with bronchi					
discoloration, tan		0	1	0	1
	- mild	0	1	0	0
	- moderate	0	0	0	1
focus/foci, black	- moderate	0	0	0	1
focus/foci, red	- mild	0	0	1	0
focus/foci, tan	- mild	2	0	0	4
focus/foci, white	- mild	0	0	0	1
mass	- present	1	0	0	0
lymph node, axillary					
discoloration, red	- mild	0	0	0	1
enlarged	- mild	0	1	0	1
not identified	- no grade	1	2	4	2
lymph node, hepatic					
not identified	- no grade	0	0	0	2
lymph node, iliac					
enlarged	- mild	0	1	0	1
not identified	- no grade	0	1	0	0
lymph node, inguinal					
absent	- no grade	1	0	0	0

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Incidences of Gross Observations - FEMALE
Terminal

Tissue / Observation	Severity	0 mg/kg/day	1 mg/kg/day	50 mg/kg/day	500 mg/kg/day
Number of Animals Examined		70	70	70	70
lymph node, inguinal					
enlarged	- mild	0	1	0	0
not identified	- no grade	19	12	16	17
lymph node, mandibular					
absent/cannibalized	- no grade	1	1	0	0
discoloration, red	- mild	1	1	1	0
enlarged	- mild	0	1	0	1
not identified	- no grade	0	0	1	0
lymph node, mediastinal					
not identified	- no grade	1	1	0	0
lymph node, mesenteric					
enlarged	- moderate	1	0	0	0
mammary gland					
swollen/thickened		8	9	8	3
	- mild	5	7	6	3
	- moderate	3	2	2	0
mediastinum					
enlarged	- moderate	0	0	0	1

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Incidences of Gross Observations - FEMALE
Terminal

Tissue / Observation	Severity	0 mg/kg/day	1 mg/kg/day	50 mg/kg/day	500 mg/kg/day
Number of Animals Examined		70	70	70	70
ovaries					
cyst		3	7	2	5
	- mild	3	5	2	4
	- moderate	0	2	0	1
mass	- present	0	0	1	0
ovaries with oviducts					
cyst	- mild	0	1	0	0
oviducts					
cyst	- mild	0	1	0	0
pancreas					
cyst	- mild	0	0	1	0
enlarged	- mild	0	0	0	1
mass	- present	1	0	0	1
parathyroid glands					
absent/cannibalized	- no grade	1	0	0	0

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Incidences of Gross Observations - FEMALE
Terminal

Tissue / Observation	Severity	0 mg/kg/day	1 mg/kg/day	50 mg/kg/day	500 mg/kg/day
Number of Animals Examined		70	70	70	70
pituitary gland					
cyst		1	1	2	1
	- mild	1	1	1	1
	- moderate	0	0	1	0
enlarged		48	59	52	35
	- minimal	1	1	0	1
	- mild	12	15	11	14
	- moderate	12	14	17	9
	- severe	23	29	24	11
salivary gland, mandibular					
absent/cannibalized	- no grade	1	1	1	0
salivary gland, parotid					
absent/cannibalized	- no grade	1	1	1	0
salivary gland, sublingual					
absent/cannibalized	- no grade	1	1	1	0
skin					
abrasion/scab		3	1	2	0
	- mild	2	1	1	0
	- moderate	1	0	1	0
absent portion/cannibalized	- no grade	1	0	0	0

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Incidences of Gross Observations - FEMALE
Terminal

Tissue / Observation	Severity	0 mg/kg/day	1 mg/kg/day	50 mg/kg/day	500 mg/kg/day
Number of Animals Examined		70	70	70	70
skin					
hair sparse		1	2	5	9
	- mild	1	1	5	5
	- moderate	0	1	0	4
nodule	- present	0	0	1	1
skin, subcutis					
abscess		0	1	0	2
	- mild	0	1	0	1
	- moderate	0	0	0	1
cyst	- moderate	0	0	0	1
mass	- present	92	93	71	59
spleen					
enlarged		2	5	4	1
	- minimal	0	1	1	0
	- mild	2	3	2	0
	- moderate	0	1	1	1
focus/foci, white	- mild	0	0	1	0
small	- mild	0	0	0	1
stomach, glandular					
focus/foci, red	- mild	0	0	0	2

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Incidences of Gross Observations - FEMALE
Terminal

Tissue / Observation	Severity	0 mg/kg/day	1 mg/kg/day	50 mg/kg/day	500 mg/kg/day
Number of Animals Examined		70	70	70	70
stomach, glandular					
swollen/thickened		0	0	0	4
	- mild	0	0	0	3
	- moderate	0	0	0	1
stomach, nonglandular					
focus/foci, tan	- mild	0	0	1	0
irregular surface	- mild	1	0	2	0
mass	- present	0	0	0	1
swollen/thickened	- mild	0	0	0	4
tail					
mass	- present	0	1	0	0
thymus					
discoloration, red	- mild	0	1	1	0
mass	- present	0	0	1	0
not identified	- no grade	1	0	0	0
small		4	2	2	4
	- mild	0	2	0	1
	- moderate	1	0	2	1
	- severe	3	0	0	2

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Incidences of Gross Observations - FEMALE
Terminal

Tissue / Observation	Severity	0 mg/kg/day	1 mg/kg/day	50 mg/kg/day	500 mg/kg/day
Number of Animals Examined		70	70	70	70
thyroid gland					
absent/cannibalized	- no grade	1	0	0	0
tongue					
absent portion/cannibalized	- no grade	1	0	0	0
focus/foci, tan	- mild	1	0	0	0
tooth/teeth					
absent/broken/malocclusion/overgrown	- no grade	1	0	0	0
trachea					
fluid, clear	- mild	0	0	0	1
urinary bladder					
distended with urine	- severe	0	1	0	0
uterus with cervix					
cyst		1	0	0	2
	- mild	1	0	0	1
	- moderate	0	0	0	1
enlarged		7	7	7	3
	- minimal	0	1	1	0
	- mild	7	4	5	3
	- moderate	0	2	1	0

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Incidences of Gross Observations - FEMALE
Terminal

Tissue / Observation	Severity	0 mg/kg/day	1 mg/kg/day	50 mg/kg/day	500 mg/kg/day
Number of Animals Examined		70	70	70	70
uterus with cervix					
focus/foci, black	- minimal	0	1	0	0
mass	- present	0	1	1	3
vagina					
prolapse		1	1	0	0
	- mild	1	0	0	0
	- moderate	0	1	0	0

Table 3
Mean Final Body and Organ Weights

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Mean Final Body and Organ Weights - MALE
Interim

	0 mg/kg/day			0.1 mg/kg/day			1 mg/kg/day			50 mg/kg/day		
Endpoint	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Body weight												
g	832	116	10	788	119	10	779	56	10	803	82	10
Brain												
g	2.319	0.088	10	2.313	0.165	10	2.241	0.124	10	2.335	0.115	10
Brain/BWt												
%	0.2837	0.0421	10	0.2986	0.0408	10	0.2889	0.0256	10	0.2939	0.0378	10
Adrenal gl												
g	0.061	0.012	10	0.069	0.016	10	0.068	0.020	10	0.074	0.023	10
Adrenal gl/BWt												
%	0.0074	0.0019	10	0.0088	0.0021	10	0.0088	0.0026	10	0.0092	0.0024	10
Adrenal gl/BrWt												
ratio	0.0263	0.0055	10	0.0299	0.0068	10	0.0306	0.0096	10	0.0318	0.0099	10

N - Number of measures used to calculate mean
SD - Standard Deviation

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Mean Final Body and Organ Weights - MALE
Interim

	0 mg/kg/day			0.1 mg/kg/day			1 mg/kg/day			50 mg/kg/day		
Endpoint	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Epididymides												
g	1.515	0.148	10	1.414	0.077	10	1.544	0.194	10	1.513	0.162	10
Epididymides/BWt %	0.1851	0.0327	10	0.1835	0.0305	10	0.1996	0.0327	10	0.1892	0.0208	10
Epididymides/BrWt ratio	0.6539	0.0671	10	0.6159	0.0708	10	0.6902	0.0885	10	0.6488	0.0721	10
Heart												
g	2.225	0.155	10	2.087	0.201	10	2.201	0.271	10	2.177	0.195	10
Heart/BWt %	0.2705	0.0308	10	0.2673	0.0214	10	0.2833	0.0362	10	0.2719	0.0192	10
Heart/BrWt ratio	0.9610	0.0820	10	0.9044	0.0918	10	0.9837	0.1173	10	0.9357	0.1078	10

N - Number of measures used to calculate mean
SD - Standard Deviation

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Mean Final Body and Organ Weights - MALE
Interim

	0 mg/kg/day			0.1 mg/kg/day			1 mg/kg/day			50 mg/kg/day		
Endpoint	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Kidneys												
g	5.819	0.838	10	5.350	0.626	10	5.207	0.499	10	5.761	0.755	10
Kidneys/BWt %	0.7032	0.0875	10	0.6862	0.0816	10	0.6699	0.0691	10	0.7170	0.0560	10
Kidneys/BrWt ratio	2.5128	0.3783	10	2.3151	0.2435	10	2.3277	0.2313	10	2.4725	0.3484	10
Liver												
g	26.919	4.939	10	26.122	4.285	10	25.522	1.906	10	29.723	4.998	10
Liver/BWt %	3.2228	0.2974	10	3.3174	0.2590	10	3.2789	0.1849	10	3.6912[b]	0.3955	10
Liver/BrWt ratio	11.6454	2.3239	10	11.2906	1.7312	10	11.4063	0.9005	10	12.7601	2.2447	10

N - Number of measures used to calculate mean
SD - Standard Deviation

[b] Significantly different from control; ($p<0.01$)

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Mean Final Body and Organ Weights - MALE
Interim

	0 mg/kg/day			0.1 mg/kg/day			1 mg/kg/day			50 mg/kg/day		
Endpoint	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Spleen												
g	1.236	0.104	10	1.069	0.138	10	1.126	0.136	10	1.222	0.231	10
Spleen/BWt												
%	0.1498	0.0131	10	0.1371	0.0177	10	0.1448	0.0185	10	0.1518	0.0213	10
Spleen/BrWt												
ratio	0.5342	0.0544	10	0.4632	0.0624	10	0.5044	0.0738	10	0.5239	0.1016	10
Testes												
g	3.687	0.357	10	3.965	0.262	10	4.057	0.567	10	4.213	0.689	10
Testes/BWt												
%	0.4512	0.0797	10	0.5140	0.0850	10	0.5255	0.0968	10	0.5272	0.0867	10
Testes/BrWt												
ratio	1.5910	0.1529	10	1.7258	0.1983	10	1.8097	0.2371	10	1.8036	0.2728	10

N - Number of measures used to calculate mean
SD - Standard Deviation

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Mean Final Body and Organ Weights - MALE
Interim

	0 mg/kg/day			0.1 mg/kg/day			1 mg/kg/day			50 mg/kg/day		
Endpoint	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Thyroid/parathyroid gl												
g	0.040	0.005	10	0.042	0.008	10	0.048	0.021	10	0.041	0.007	10
Thyroid/parathyroid gl/BWt %	0.0049	0.0009	10	0.0054	0.0012	10	0.0062	0.0026	10	0.0051	0.0005	10
Thyroid/parathyroid gl/BrWt ratio	0.0173	0.0028	10	0.0182	0.0034	10	0.0212	0.0083	10	0.0178	0.0030	10

N - Number of measures used to calculate mean
SD - Standard Deviation

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Mean Final Body and Organ Weights - FEMALE
Interim

	0 mg/kg/day			1 mg/kg/day			50 mg/kg/day			500 mg/kg/day		
Endpoint	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Body weight												
g	451	71	10	405	59	10	445	87	10	363[a]	52	10
Brain												
g	1.968	0.112	10	1.980	0.074	10	1.996	0.077	10	1.930	0.063	10
Brain/BWt												
%	0.4442	0.0604	10	0.4971	0.0638	10	0.4659	0.1041	10	0.5426[a]	0.0864	10
Adrenal gl												
g	0.079	0.021	10	0.077	0.022	10	0.091	0.017	10	0.098	0.074	10
Adrenal gl/BWt												
%	0.0175	0.0040	10	0.0196	0.0074	10	0.0210	0.0054	10	0.0265	0.0180	10
Adrenal gl/BrWt												
ratio	0.0401	0.0111	10	0.0391	0.0123	10	0.0457	0.0088	10	0.0513	0.0413	10

N - Number of measures used to calculate mean
SD - Standard Deviation

[a] Significantly different from control; ($p<0.05$)

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Mean Final Body and Organ Weights - FEMALE
Interim

	0 mg/kg/day			1 mg/kg/day			50 mg/kg/day			500 mg/kg/day		
Endpoint	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Heart												
g	1.439	0.365	10	1.253	0.069	10	1.324	0.213	10	1.222	0.138	10
Heart/BWt %	0.3167	0.0362	10	0.3134	0.0311	10	0.3010	0.0333	10	0.3396	0.0327	10
Heart/BrWt ratio	0.7361	0.2120	10	0.6331	0.0350	10	0.6652	0.1162	10	0.6336	0.0687	10
Kidneys												
g	2.850	0.520	10	2.695	0.190	10	2.963	0.347	10	2.807	0.245	10
Kidneys/BWt %	0.6308	0.0383	10	0.6753	0.0867	10	0.6828	0.1139	10	0.7855[b]	0.1085	10
Kidneys/BrWt ratio	1.4531	0.3011	10	1.3621	0.1025	10	1.4876	0.1943	10	1.4560	0.1361	10

N - Number of measures used to calculate mean
SD - Standard Deviation

[b] Significantly different from control; ($p<0.01$)

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Mean Final Body and Organ Weights - FEMALE
Interim

	0 mg/kg/day			1 mg/kg/day			50 mg/kg/day			500 mg/kg/day		
Endpoint	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Liver												
g	13.200	2.508	10	11.961	1.570	10	14.754	3.576	10	17.589[b]	2.580	10
Liver/BWt %	2.9249	0.2519	10	2.9744	0.3031	10	3.3096	0.3748	10	4.8773[b]	0.5557	10
Liver/BrWt ratio	6.7391	1.4803	10	6.0364	0.7165	10	7.4088	1.8336	10	9.1168[b]	1.2927	10
Ovaries w/ oviducts												
g	0.105	0.013	10	0.121	0.042	10	0.134	0.043	10	0.119	0.056	10
Ovaries w/ oviducts/BWt %	0.0234	0.0026	10	0.0308	0.0128	10	0.0306	0.0093	10	0.0324	0.0129	10
Ovaries w/ oviducts/BrWt ratio	0.0533	0.0064	10	0.0613	0.0218	10	0.0671	0.0214	10	0.0612	0.0278	10

N - Number of measures used to calculate mean
SD - Standard Deviation

[b] Significantly different from control; (p<0.01)

MPI Research Study Number 125-141
Dupont-18405-1238
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Mean Final Body and Organ Weights - FEMALE
Interim

	0 mg/kg/day			1 mg/kg/day			50 mg/kg/day			500 mg/kg/day		
Endpoint	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Spleen												
g	0.694	0.086	10	0.613	0.063	10	0.614	0.110	10	0.566[b]	0.080	10
Spleen/BWt												
%	0.1548	0.0118	10	0.1533	0.0212	10	0.1418	0.0375	10	0.1571	0.0196	10
Spleen/BrWt												
ratio	0.3536	0.0498	10	0.3098	0.0312	10	0.3083	0.0576	10	0.2936[a]	0.0413	10
Thyroid/parathyroid gl												
g	0.029	0.007	10	0.025	0.004	10	0.031	0.010	10	0.029	0.006	10
Thyroid/parathyroid gl/BWt												
%	0.0063	0.0011	10	0.0063	0.0008	10	0.0070	0.0016	10	0.0081[b]	0.0014	10
Thyroid/parathyroid gl/BrWt												
ratio	0.0146	0.0036	10	0.0128	0.0022	10	0.0156	0.0053	10	0.0152	0.0031	10

N - Number of measures used to calculate mean
SD - Standard Deviation

[a] Significantly different from control; ($p<0.05$)
[b] Significantly different from control; ($p<0.01$)

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Mean Final Body and Organ Weights - FEMALE
Interim

	0 mg/kg/day			1 mg/kg/day			50 mg/kg/day			500 mg/kg/day		
Endpoint	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Uterus w/ cervix												
g	0.889	0.241	10	0.910	0.271	10	1.172	0.197	10	1.068	0.476	10
Uterus w/ cervix/BWt %	0.2008	0.0629	10	0.2316	0.0890	10	0.2703	0.0577	10	0.2994	0.1420	10
Uterus w/ cervix/BrWt ratio	0.4542	0.1294	10	0.4631	0.1556	10	0.5860	0.0914	10	0.5553	0.2460	10

N - Number of measures used to calculate mean
SD - Standard Deviation

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Mean Final Body and Organ Weights - MALE
Terminal

	0 mg/kg/day			0.1 mg/kg/day			1 mg/kg/day			50 mg/kg/day		
Endpoint	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Body weight												
g	830	111	15	837	159	20	763	132	18	840	97	18
Brain												
g	2.339	0.182	15	2.311	0.154	20	2.302	0.092	18	2.340	0.117	18
Brain/BWt												
%	0.2852	0.0313	15	0.2849	0.0538	20	0.3110	0.0617	18	0.2815	0.0291	18
Adrenal gl												
g	0.092	0.015	14	0.094	0.030	17	0.086	0.028	18	0.089	0.027	16
Adrenal gl/BWt												
%	0.0114	0.0029	14	0.0115	0.0040	17	0.0113	0.0031	18	0.0109	0.0033	16
Adrenal gl/BrWt												
ratio	0.0394	0.0076	14	0.0411	0.0133	17	0.0373	0.0117	18	0.0379	0.0111	16

N - Number of measures used to calculate mean
SD - Standard Deviation

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Mean Final Body and Organ Weights - MALE
Terminal

	0 mg/kg/day			0.1 mg/kg/day			1 mg/kg/day			50 mg/kg/day		
Endpoint	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Epididymides												
g	1.410	0.194	15	1.392	0.161	20	1.343	0.236	18	1.435	0.187	18
Epididymides/BWt %	0.1723	0.0316	15	0.1691	0.0198	20	0.1794	0.0359	18	0.1731	0.0320	18
Epididymides/BrWt ratio	0.6071	0.1041	15	0.6036	0.0730	20	0.5843	0.1068	18	0.6141	0.0854	18
Heart												
g	2.186	0.199	15	2.277	0.252	20	2.178	0.346	18	2.259	0.369	18
Heart/BWt %	0.2670	0.0366	15	0.2781	0.0428	20	0.2929	0.0668	18	0.2700	0.0366	18
Heart/BrWt ratio	0.9393	0.1060	15	0.9870	0.1066	20	0.9461	0.1437	18	0.9655	0.1522	18

N - Number of measures used to calculate mean
SD - Standard Deviation

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Mean Final Body and Organ Weights - MALE
Terminal

	0 mg/kg/day			0.1 mg/kg/day			1 mg/kg/day			50 mg/kg/day		
Endpoint	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Kidneys												
g	5.938	0.740	15	6.209	1.203	19	6.275	1.717	18	6.084	1.211	18
Kidneys/BWt %	0.7236	0.1060	15	0.7552	0.2032	19	0.8419	0.2547	18	0.7232	0.1180	18
Kidneys/BrWt ratio	2.5464	0.3161	15	2.6851	0.5375	19	2.7268	0.7469	18	2.5921	0.4572	18
Liver												
g	24.291	3.642	15	26.589	6.407	20	24.112	5.638	18	27.057	4.821	18
Liver/BWt %	2.9434	0.3864	15	3.2961	1.2542	20	3.2048	0.7362	18	3.2266	0.4828	18
Liver/BrWt ratio	10.4258	1.6423	15	11.5472	2.9932	20	10.4943	2.5074	18	11.5460	1.8170	18

N - Number of measures used to calculate mean
SD - Standard Deviation

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Mean Final Body and Organ Weights - MALE
Terminal

	0 mg/kg/day			0.1 mg/kg/day			1 mg/kg/day			50 mg/kg/day		
Endpoint	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Spleen												
g	1.192	0.270	15	1.347	0.270	20	1.372	0.387	18	1.223	0.194	18
Spleen/BWt %	0.1440	0.0273	15	0.1671	0.0551	20	0.1847[a]	0.0659	18	0.1468	0.0271	18
Spleen/BrWt ratio	0.5100	0.1075	15	0.5838	0.1167	20	0.5959	0.1649	18	0.5247	0.0943	18
Testes												
g	3.733	0.368	15	3.682	0.514	20	3.746	0.825	18	4.074	0.828	18
Testes/BWt %	0.4570	0.0716	15	0.4508	0.0817	20	0.5073	0.1585	18	0.4913	0.1118	18
Testes/BrWt ratio	1.6057	0.2091	15	1.5940	0.2015	20	1.6344	0.3935	18	1.7472	0.3782	18

N - Number of measures used to calculate mean
SD - Standard Deviation

[a] Significantly different from control; ($p<0.05$)

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Mean Final Body and Organ Weights - MALE
Terminal

	0 mg/kg/day			0.1 mg/kg/day			1 mg/kg/day			50 mg/kg/day		
Endpoint	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Thyroid/parathyroid gl												
g	0.058	0.040	15	0.063	0.036	19	0.044	0.011	18	0.054	0.023	18
Thyroid/parathyroid gl/BWt %	0.0068	0.0038	15	0.0078	0.0051	19	0.0059	0.0013	18	0.0066	0.0033	18
Thyroid/parathyroid gl/BrWt ratio	0.0246	0.0170	15	0.0270	0.0141	19	0.0192	0.0042	18	0.0233	0.0103	18

N - Number of measures used to calculate mean
SD - Standard Deviation

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Mean Final Body and Organ Weights - FEMALE
Terminal

	0 mg/kg/day			1 mg/kg/day			50 mg/kg/day			500 mg/kg/day		
Endpoint	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Body weight												
g	462	75	16	482	99	22	519	69	15	457	86	18
Brain												
g	1.993	0.105	16	2.029	0.097	22	1.985	0.123	15	2.400	1.719	18
Brain/BWt												
%	0.4418	0.0727	16	0.4393	0.0984	22	0.3885	0.0520	15	0.5329	0.3531	18
Adrenal gl												
g	0.100	0.030	16	0.101	0.038	22	0.116	0.057	14	0.126	0.096	18
Adrenal gl/BWt												
%	0.0216	0.0053	16	0.0217	0.0090	22	0.0228	0.0114	14	0.0282	0.0224	18
Adrenal gl/BrWt												
ratio	0.0499	0.0140	16	0.0497	0.0187	22	0.0589	0.0298	14	0.0609	0.0447	18

N - Number of measures used to calculate mean
SD - Standard Deviation

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Mean Final Body and Organ Weights - FEMALE
Terminal

	0 mg/kg/day			1 mg/kg/day			50 mg/kg/day			500 mg/kg/day		
Endpoint	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Heart												
g	1.438	0.202	16	1.418	0.207	22	1.601	0.318	15	1.501	0.235	18
Heart/BWt %	0.3144	0.0373	16	0.3039	0.0712	22	0.3112	0.0628	15	0.3328	0.0448	18
Heart/BrWt ratio	0.7221	0.0983	16	0.7020	0.1183	22	0.8061	0.1445	15	0.7211	0.1888	18
Kidneys												
g	3.103	0.348	16	3.185	0.407	21	3.247	0.352	14	3.517[a]	0.573	18
Kidneys/BWt %	0.6839	0.1033	16	0.6664	0.1256	21	0.6352	0.1018	14	0.7790[a]	0.1023	18
Kidneys/BrWt ratio	1.5560	0.1379	16	1.5659	0.2059	21	1.6461	0.1906	14	1.6928	0.4345	18

N - Number of measures used to calculate mean
SD - Standard Deviation

[a] Significantly different from control; ($p<0.05$)

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H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Mean Final Body and Organ Weights - FEMALE
Terminal

	0 mg/kg/day			1 mg/kg/day			50 mg/kg/day			500 mg/kg/day		
Endpoint	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Liver												
g	16.379	3.783	16	15.802	4.257	22	17.215	3.041	15	23.232[b]	8.181	18
Liver/BWt %	3.5154	0.4327	16	3.3040	0.6869	22	3.3387	0.5578	15	4.9782[b]	0.8934	18
Liver/BrWt ratio	8.2118	1.8579	16	7.8181	2.2269	22	8.6551	1.2959	15	11.0377[a]	4.3882	18
Ovaries w/ oviducts												
g	0.124	0.039	16	0.149	0.120	22	0.114	0.029	15	0.159	0.082	18
Ovaries w/ oviducts/BWt %	0.0270	0.0075	16	0.0311	0.0221	22	0.0223	0.0061	15	0.0355	0.0170	18
Ovaries w/ oviducts/BrWt ratio	0.0623	0.0201	16	0.0727	0.0552	22	0.0577	0.0145	15	0.0770	0.0440	18

N - Number of measures used to calculate mean
SD - Standard Deviation

[a] Significantly different from control; (p<0.05)
[b] Significantly different from control; (p<0.01)

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H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Mean Final Body and Organ Weights - FEMALE
Terminal

	0 mg/kg/day			1 mg/kg/day			50 mg/kg/day			500 mg/kg/day		
Endpoint	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Spleen												
g	0.911	0.331	16	0.811	0.289	22	1.023	0.724	15	0.671	0.185	17
Spleen/BWt %	0.1947	0.0574	16	0.1714	0.0574	22	0.1997	0.1438	15	0.1481	0.0304	17
Spleen/BrWt ratio	0.4563	0.1642	16	0.4004	0.1447	22	0.5095	0.3399	15	0.3359	0.0903	17
Thyroid/parathyroid gl												
g	0.041	0.013	16	0.045	0.014	22	0.042	0.006	15	0.040	0.007	18
Thyroid/parathyroid gl/BWt %	0.0089	0.0021	16	0.0099	0.0037	22	0.0083	0.0018	15	0.0090	0.0018	18
Thyroid/parathyroid gl/BrWt ratio	0.0208	0.0061	16	0.0224	0.0071	22	0.0215	0.0037	15	0.0195	0.0052	18

N - Number of measures used to calculate mean
SD - Standard Deviation

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Mean Final Body and Organ Weights - FEMALE
Terminal

	0 mg/kg/day			1 mg/kg/day			50 mg/kg/day			500 mg/kg/day		
Endpoint	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Uterus w/ cervix												
g	1.801	2.012	16	1.185	0.718	22	1.276	0.716	15	1.107	0.403	18
Uterus w/ cervix/BWt												
%	0.4411	0.6526	16	0.2678	0.2072	22	0.2511	0.1488	15	0.2506	0.1084	18
Uterus w/ cervix/BrWt												
ratio	0.9179	1.0874	16	0.5858	0.3620	22	0.6405	0.3514	15	0.5418	0.2306	18

N - Number of measures used to calculate mean
SD - Standard Deviation

Table 4
Incidences of Microscopic Observations

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Incidences of Microscopic Observations - MALE
Interim

Tissue / Observation	Severity	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
Number of Animals Examined		10	10	10	10
adrenal glands		(10)	(0)	(0)	(10)
hyperplasia, focal cortical	- mild	0	0	0	1
hyperplasia, focal medullary	- mild	0	0	0	1
vacuolation, diffuse	- minimal	0	0	0	1
vacuolation, focal	- minimal	0	0	0	1
within normal limits		10	0	0	8
aorta		(10)	(0)	(0)	(10)
within normal limits		10	0	0	10
bone marrow, femur		(10)	(0)	(0)	(10)
within normal limits		10	0	0	10
bone marrow, sternum		(10)	(0)	(0)	(10)
within normal limits		10	0	0	10
bone, femur		(10)	(0)	(0)	(10)
within normal limits		10	0	0	10
bone, sternum		(10)	(0)	(0)	(10)
within normal limits		10	0	0	10

( ) - Number observed

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Incidences of Microscopic Observations - MALE
Interim

Tissue / Observation	Severity	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
Number of Animals Examined		10	10	10	10
brain		(10)	(0)	(0)	(10)
astrocytoma, malignant, primary		1	0	0	0
compression, ventral (pituitary tumor)	- minimal	1	0	0	0
within normal limits		8	0	0	10
coagulating glands		(10)	(0)	(0)	(10)
within normal limits		10	0	0	10
epididymides		(10)	(0)	(0)	(10)
oligospermia/germ cell debris, unilateral	- mild	0	0	0	1
within normal limits		10	0	0	9
esophagus		(10)	(0)	(0)	(10)
within normal limits		10	0	0	10
eyes		(10)	(1)	(0)	(10)
phthisis bulbi	- severe	0	1	0	0
within normal limits		10	0	0	10
eyes, optic nerves		(10)	(0)	(0)	(10)
within normal limits		10	0	0	10

( ) - Number observed

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Incidences of Microscopic Observations - MALE
Interim

Tissue / Observation	Severity	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
Number of Animals Examined		10	10	10	10
eyes, retina		(10)	(0)	(0)	(10)
degeneration/atrophy, retina, unilateral	- minimal	1	0	0	0
within normal limits		9	0	0	10
galt		(10)	(0)	(0)	(10)
within normal limits		10	0	0	10
harderian glands		(10)	(1)	(0)	(10)
hyperplasia, focal	- minimal	0	0	0	1
within normal limits		10	1	0	9
heart		(10)	(0)	(0)	(10)
cardiomyopathy		7	0	0	7
	- minimal	7	0	0	5
	- mild	0	0	0	2
within normal limits		3	0	0	3
joint, tibiofemoral		(10)	(0)	(0)	(10)
within normal limits		10	0	0	10
kidneys		(10)	(0)	(0)	(10)
hydronephrosis, bilateral	- mild	0	0	0	1
hydronephrosis, unilateral	- mild	0	0	0	1

( ) - Number observed

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Incidences of Microscopic Observations - MALE
Interim

Tissue / Observation	Severity	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
Number of Animals Examined		10	10	10	10
kidneys		(10)	(0)	(0)	(10)
inflammation, acute	- mild	1	0	0	0
mineralization, pelvic	- mild	0	0	0	1
nephropathy, chronic progressive		9	0	0	7
	- minimal	2	0	0	3
	- mild	4	0	0	4
	- moderate	3	0	0	0
within normal limits		1	0	0	3
lacrimal glands, exorbital		(10)	(0)	(0)	(10)
within normal limits		10	0	0	10
large intestine, cecum		(10)	(0)	(0)	(10)
within normal limits		10	0	0	10
large intestine, colon		(10)	(0)	(0)	(10)
within normal limits		10	0	0	10
large intestine, rectum		(10)	(0)	(0)	(10)
within normal limits		10	0	0	10
larynx		(10)	(0)	(0)	(10)
within normal limits		10	0	0	10

( ) - Number observed

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Incidences of Microscopic Observations - MALE
Interim

Tissue / Observation	Severity	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
Number of Animals Examined		10	10	10	10
liver		(10)	(10)	(10)	(10)
degeneration, cystic, focal	- minimal	0	0	0	3
dilatation, sinusoidal	- minimal	0	0	1	0
focus of cellular alteration, clear	- minimal	0	3	0	1
focus of cellular alteration, eosinophilic	- minimal	0	1	0	0
hyperplasia, bile duct	- minimal	0	0	1	1
infiltration, mononuclear cell	- minimal	8	8	7	4
necrosis, focal		1	1	0	5
	- minimal	1	1	0	4
	- mild	0	0	0	1
polyarteritis	- minimal	0	0	1	0
vacuolation, centrilobular	- minimal	4	0	0	2
vacuolation, focal	- minimal	1	0	0	1
vacuolation, periportal	- minimal	1	0	0	0
within normal limits		0	1	3	0
lung		(10)	(0)	(0)	(10)
histiocytosis, alveolar	- minimal	0	0	0	2
hyperplasia, type II cell	- minimal	1	0	0	0
within normal limits		9	0	0	8

( ) - Number observed

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Incidences of Microscopic Observations - MALE
Interim

Tissue / Observation	Severity	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
Number of Animals Examined		10	10	10	10
lymph node, iliac		(0)	(1)	(0)	(0)
within normal limits		0	1	0	0
lymph node, mandibular		(10)	(0)	(0)	(10)
within normal limits		10	0	0	10
lymph node, mesenteric		(10)	(0)	(0)	(10)
hemangiosarcoma, malignant, primary		1	0	0	0
within normal limits		9	0	0	10
mesentery/peritoneum		(0)	(1)	(0)	(0)
necrosis, fat	- moderate	0	1	0	0
nerve, sciatic		(10)	(0)	(0)	(10)
within normal limits		10	0	0	10
nose, level a		(10)	(0)	(0)	(10)
within normal limits		10	0	0	10
nose, level b		(10)	(0)	(0)	(10)
within normal limits		10	0	0	10

( ) - Number observed

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Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Incidences of Microscopic Observations - MALE
Interim

Tissue / Observation	Severity	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
Number of Animals Examined		10	10	10	10
nose, level c		(10)	(0)	(0)	(10)
within normal limits		10	0	0	10
nose, level d		(10)	(0)	(0)	(10)
odontitis/periodontitis	- mild	1	0	0	0
within normal limits		9	0	0	10
pancreas		(10)	(0)	(0)	(10)
atrophy, acinar	- minimal	0	0	0	2
fibrosis	- minimal	6	0	0	1
within normal limits		4	0	0	7
parathyroid glands		(8)	(0)	(0)	(7)
within normal limits		8	0	0	7
pharynx		(10)	(0)	(0)	(10)
within normal limits		10	0	0	10
pituitary gland		(10)	(0)	(0)	(10)
adenoma, pars distalis, benign, primary		3	0	0	3
cyst	- mild	1	0	0	0

( ) - Number observed

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H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Incidences of Microscopic Observations - MALE
Interim

Tissue / Observation	Severity	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
Number of Animals Examined		10	10	10	10
pituitary gland		(10)	(0)	(0)	(10)
hyperplasia, focal, pars distalis		2	0	0	4
	- minimal	1	0	0	1
	- mild	1	0	0	3
within normal limits		5	0	0	3
prostate gland		(10)	(0)	(0)	(10)
within normal limits		10	0	0	10
salivary gland, mandibular		(10)	(0)	(0)	(10)
within normal limits		10	0	0	10
salivary gland, parotid		(10)	(0)	(0)	(10)
within normal limits		10	0	0	10
salivary gland, sublingual		(10)	(0)	(0)	(10)
within normal limits		10	0	0	10
seminal vesicles		(10)	(1)	(0)	(10)
dilatation	- mild	0	1	0	0
inflammation	- minimal	0	1	0	0
within normal limits		10	0	0	10

( ) - Number observed

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H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Incidences of Microscopic Observations - MALE
Interim

Tissue / Observation	Severity	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
Number of Animals Examined		10	10	10	10
skeletal muscle, biceps femoris		(10)	(0)	(0)	(10)
within normal limits		10	0	0	10
skin		(10)	(2)	(0)	(10)
alopecia/hypotrichosis		1	1	0	0
	- minimal	0	1	0	0
	- moderate	1	0	0	0
granuloma, foreign body	- mild	0	0	0	1
hyperplasia, epidermal	- mild	1	0	0	0
papilloma, squamous cell, benign, primary		0	1	0	0
within normal limits		9	0	0	9
small intestine, duodenum		(10)	(0)	(0)	(10)
within normal limits		10	0	0	10
small intestine, ileum		(10)	(0)	(0)	(10)
within normal limits		10	0	0	10
small intestine, jejunum		(10)	(0)	(0)	(10)
within normal limits		10	0	0	10
spinal cord, cervical		(10)	(0)	(0)	(10)
within normal limits		10	0	0	10

( ) - Number observed

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Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Incidences of Microscopic Observations - MALE
Interim

Tissue / Observation	Severity	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
Number of Animals Examined		10	10	10	10
spinal cord, lumbar		(10)	(0)	(0)	(10)
within normal limits		10	0	0	10
spinal cord, thoracic		(10)	(0)	(0)	(10)
within normal limits		10	0	0	10
spleen		(10)	(0)	(0)	(10)
within normal limits		10	0	0	10
stomach, glandular		(10)	(0)	(0)	(10)
within normal limits		10	0	0	10
stomach, nonglandular		(10)	(0)	(0)	(10)
within normal limits		10	0	0	10
testes		(10)	(10)	(10)	(10)
adenoma, interstitial cell, benign, primary		0	0	0	1
degeneration/atrophy, seminiferous tubules, unilateral	- mild	0	0	0	1
hyperplasia, interstitial cell	- minimal	1	0	0	3
mineralization, tubular	- mild	0	0	0	1
within normal limits		9	10	10	5

( ) - Number observed

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Incidences of Microscopic Observations - MALE
Interim

Tissue / Observation	Severity	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
Number of Animals Examined		10	10	10	10
thymus		(10)	(0)	(0)	(10)
depletion, lymphoid, generalized		9	0	0	10
	- moderate	8	0	0	10
	- severe	1	0	0	0
within normal limits		1	0	0	0
thyroid gland		(10)	(0)	(1)	(10)
carcinoma, follicular cell, malignant, primary		0	0	1	0
within normal limits		10	0	0	10
tongue		(10)	(0)	(0)	(10)
within normal limits		10	0	0	10
trachea		(10)	(0)	(0)	(10)
within normal limits		10	0	0	10
ureters		(10)	(0)	(0)	(10)
dilatation	- mild	0	0	0	1
within normal limits		10	0	0	9
urinary bladder		(10)	(0)	(0)	(10)
within normal limits		10	0	0	10

( ) - Number observed

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H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Incidences of Microscopic Observations - FEMALE
Interim

Tissue / Observation	Severity	0 mg/kg/day	1 mg/kg/day	50 mg/kg/day	500 mg/kg/day
Number of Animals Examined		10	10	10	10
adrenal glands		(10)	(0)	(0)	(10)
angiectasis/cystic degeneration, focal cortical		7	0	0	5
	- minimal	4	0	0	4
	- mild	3	0	0	1
hyperplasia, focal cortical	- mild	0	0	0	1
within normal limits		3	0	0	4
aorta		(10)	(0)	(0)	(10)
within normal limits		10	0	0	10
bone marrow, femur		(10)	(0)	(0)	(10)
within normal limits		10	0	0	10
bone marrow, sternum		(10)	(0)	(0)	(10)
within normal limits		10	0	0	10
bone, femur		(10)	(0)	(0)	(10)
within normal limits		10	0	0	10
bone, sternum		(10)	(0)	(0)	(10)
within normal limits		10	0	0	10

( ) - Number observed

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Incidences of Microscopic Observations - FEMALE
Interim

Tissue / Observation	Severity	0 mg/kg/day	1 mg/kg/day	50 mg/kg/day	500 mg/kg/day
Number of Animals Examined		10	10	10	10
brain		(10)	(0)	(0)	(10)
compression, ventral (pituitary tumor)	- moderate	0	0	0	1
within normal limits		10	0	0	9
esophagus		(10)	(0)	(0)	(10)
within normal limits		10	0	0	10
eyes		(10)	(0)	(0)	(10)
within normal limits		10	0	0	10
eyes, optic nerves		(10)	(0)	(0)	(10)
within normal limits		10	0	0	10
eyes, retina		(10)	(0)	(0)	(10)
within normal limits		10	0	0	10
galt		(10)	(0)	(0)	(10)
within normal limits		10	0	0	10
harderian glands		(10)	(0)	(0)	(10)
within normal limits		10	0	0	10

( ) - Number observed

MPI Research Study Number 125-141
Dupont-18405-1238
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Incidences of Microscopic Observations - FEMALE
Interim

Tissue / Observation	Severity	0 mg/kg/day	1 mg/kg/day	50 mg/kg/day	500 mg/kg/day
Number of Animals Examined		10	10	10	10
heart		(10)	(0)	(0)	(10)
cardiomyopathy	- minimal	1	0	0	0
within normal limits		9	0	0	10
joint, tibiofemoral		(10)	(0)	(0)	(10)
within normal limits		10	0	0	10
kidneys		(10)	(10)	(10)	(10)
mineralization, pelvic	- minimal	6	5	7	9
mineralization, tubular	- minimal	3	3	1	8
nephropathy, chronic progressive		6	4	6	9
	- minimal	5	3	4	3
	- mild	0	1	2	6
	- moderate	1	0	0	0
pyelitis	- minimal	0	1	0	0
within normal limits		2	2	0	0
lacrimal glands, exorbital		(10)	(0)	(0)	(10)
within normal limits		10	0	0	10
large intestine, cecum		(10)	(0)	(0)	(10)
within normal limits		10	0	0	10

( ) - Number observed

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Incidences of Microscopic Observations - FEMALE
Interim

Tissue / Observation	Severity	0 mg/kg/day	1 mg/kg/day	50 mg/kg/day	500 mg/kg/day
Number of Animals Examined		10	10	10	10
large intestine, colon		(10)	(0)	(0)	(10)
within normal limits		10	0	0	10
large intestine, rectum		(10)	(0)	(0)	(10)
within normal limits		10	0	0	10
larynx		(10)	(0)	(0)	(10)
within normal limits		10	0	0	10
liver		(10)	(10)	(10)	(10)
degeneration, cystic, focal	- minimal	0	0	1	0
dilatation, sinusoidal	- minimal	0	0	1	0
focus of cellular alteration, basophilic	- minimal	1	2	1	0
focus of cellular alteration, clear	- minimal	1	0	0	0
focus of cellular alteration, eosinophilic		1	0	2	0
	- minimal	1	0	1	0
	- mild	0	0	1	0
hyperplasia, bile duct		3	2	1	3
	- minimal	2	2	1	3
	- mild	1	0	0	0
hypertrophy, hepatocyte, centrilobular		0	0	0	10
	- minimal	0	0	0	5
	- mild	0	0	0	5

( ) - Number observed

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Incidences of Microscopic Observations - FEMALE
Interim

Tissue / Observation	Severity	0 mg/kg/day	1 mg/kg/day	50 mg/kg/day	500 mg/kg/day
Number of Animals Examined		10	10	10	10
liver		(10)	(10)	(10)	(10)
infiltration, mononuclear cell	- minimal	2	5	2	2
necrosis, focal	- minimal	0	0	0	1
vacuolation, median cleft	- minimal	1	0	0	0
within normal limits		3	4	4	0
lung		(10)	(1)	(0)	(10)
histiocytosis, alveolar	- minimal	4	1	0	5
within normal limits		6	0	0	5
lymph node, axillary		(0)	(1)	(1)	(0)
within normal limits		0	1	1	0
lymph node, inguinal		(0)	(0)	(1)	(2)
within normal limits		0	0	1	2
lymph node, mandibular		(10)	(0)	(0)	(10)
within normal limits		10	0	0	10
lymph node, mesenteric		(10)	(0)	(0)	(10)
within normal limits		10	0	0	10

( ) - Number observed

MPI Research Study Number 125-141
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H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Incidences of Microscopic Observations - FEMALE
Interim

Tissue / Observation	Severity	0 mg/kg/day	1 mg/kg/day	50 mg/kg/day	500 mg/kg/day
Number of Animals Examined		10	10	10	10
mammary gland		(10)	(2)	(2)	(10)
adenocarcinoma, malignant, primary		1	1	0	1
adenoma, benign, primary		0	0	1	0
fibroadenoma, benign, primary		0	0	2	1
hyperplasia, lobular		10	1	1	10
	- minimal	7	0	0	7
	- mild	3	1	1	3
mesentery/peritoneum		(0)	(0)	(1)	(0)
necrosis, fat	- mild	0	0	1	0
nerve, sciatic		(10)	(0)	(0)	(10)
within normal limits		10	0	0	10
nose, level a		(10)	(0)	(0)	(10)
within normal limits		10	0	0	10
nose, level b		(10)	(0)	(0)	(10)
within normal limits		10	0	0	10
nose, level c		(10)	(0)	(0)	(10)
within normal limits		10	0	0	10

( ) - Number observed

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Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Incidences of Microscopic Observations - FEMALE
Interim

Tissue / Observation	Severity	0 mg/kg/day	1 mg/kg/day	50 mg/kg/day	500 mg/kg/day
Number of Animals Examined		10	10	10	10
nose, level d		(10)	(0)	(0)	(10)
within normal limits		10	0	0	10
ovaries		(10)	(0)	(1)	(10)
within normal limits		10	0	1	10
oviducts		(10)	(0)	(0)	(10)
within normal limits		10	0	0	10
pancreas		(10)	(0)	(0)	(10)
within normal limits		10	0	0	10
parathyroid glands		(6)	(0)	(0)	(7)
within normal limits		6	0	0	7
pharynx		(10)	(0)	(0)	(10)
within normal limits		10	0	0	10
pituitary gland		(10)	(6)	(4)	(10)
adenoma, pars distalis, benign, primary		2	3	1	2
hyperplasia, diffuse, pars distalis	- mild	1	1	0	0
hyperplasia, focal, pars distalis	- mild	0	1	0	1
within normal limits		7	1	3	7

( ) - Number observed

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Incidences of Microscopic Observations - FEMALE
Interim

Tissue / Observation	Severity	0 mg/kg/day	1 mg/kg/day	50 mg/kg/day	500 mg/kg/day
Number of Animals Examined		10	10	10	10
salivary gland, mandibular		(10)	(0)	(0)	(10)
within normal limits		10	0	0	10
salivary gland, parotid		(10)	(0)	(0)	(10)
within normal limits		10	0	0	10
salivary gland, sublingual		(10)	(0)	(0)	(10)
within normal limits		10	0	0	10
skeletal muscle, biceps femoris		(10)	(0)	(0)	(10)
within normal limits		10	0	0	10
skin		(10)	(2)	(2)	(10)
alopecia/hypotrichosis		1	2	2	2
	- mild	0	1	2	2
	- moderate	1	1	0	0
within normal limits		9	0	0	8
small intestine, duodenum		(10)	(0)	(0)	(10)
within normal limits		10	0	0	10

( ) - Number observed

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H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Incidences of Microscopic Observations - FEMALE
Interim

Tissue / Observation	Severity	0 mg/kg/day	1 mg/kg/day	50 mg/kg/day	500 mg/kg/day
Number of Animals Examined		10	10	10	10
small intestine, ileum		(10)	(0)	(0)	(10)
within normal limits		10	0	0	10
small intestine, jejunum		(10)	(0)	(0)	(10)
within normal limits		10	0	0	10
spinal cord, cervical		(10)	(0)	(0)	(10)
within normal limits		10	0	0	10
spinal cord, lumbar		(10)	(0)	(0)	(10)
within normal limits		10	0	0	10
spinal cord, thoracic		(10)	(0)	(0)	(10)
within normal limits		10	0	0	10
spleen		(10)	(0)	(1)	(10)
within normal limits		10	0	1	10
stomach, glandular		(10)	(0)	(0)	(10)
within normal limits		10	0	0	10
stomach, nonglandular		(10)	(0)	(0)	(10)
cyst, keratin	- mild	0	0	0	1

( ) - Number observed

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H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Incidences of Microscopic Observations - FEMALE
Interim

Tissue / Observation	Severity	0 mg/kg/day	1 mg/kg/day	50 mg/kg/day	500 mg/kg/day
Number of Animals Examined		10	10	10	10
stomach, nonglandular		(10)	(0)	(0)	(10)
within normal limits		10	0	0	9
thymus		(10)	(0)	(0)	(10)
depletion, lymphoid, generalized	- moderate	10	0	0	10
thyroid gland		(10)	(0)	(0)	(10)
adenoma, c-cell, benign, primary		1	0	0	0
hyperplasia, c-cell, focal	- minimal	0	0	0	1
within normal limits		9	0	0	9
tongue		(10)	(0)	(0)	(10)
hyperplasia, squamous cell	- moderate	1	0	0	0
inflammation, subacute/chronic	- mild	1	0	0	0
within normal limits		9	0	0	10
trachea		(10)	(0)	(0)	(10)
within normal limits		10	0	0	10
ureters		(10)	(0)	(0)	(10)
within normal limits		10	0	0	10

( ) - Number observed

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H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Incidences of Microscopic Observations - FEMALE
Interim

Tissue / Observation	Severity	0 mg/kg/day	1 mg/kg/day	50 mg/kg/day	500 mg/kg/day
Number of Animals Examined		10	10	10	10
urinary bladder		(10)	(0)	(0)	(10)
within normal limits		10	0	0	10
uterus with cervix		(10)	(0)	(0)	(10)
cyst	- mild	0	0	0	1
dilatation, gland/lumen	- mild	0	0	0	1
hyperplasia, cervical fibromuscular	- moderate	0	0	0	1
metaplasia, squamous	- minimal	3	0	0	0
within normal limits		7	0	0	8
vagina		(10)	(0)	(0)	(10)
within normal limits		10	0	0	10

( ) - Number observed

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Incidences of Microscopic Observations - MALE
Terminal

Tissue / Observation	Severity	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
Number of Animals Examined		70	70	70	70
adipose tissue		(0)	(0)	(1)	(0)
within normal limits		0	0	1	0
adrenal glands		(70)	(52)	(52)	(70)
adenoma, cortical, benign, primary		2	0	1	1
angiectasis/cystic degeneration, focal cortical		17	3	1	14
	- minimal	10	0	1	11
	- mild	4	3	0	2
	- moderate	3	0	0	1
atrophy, cortical		1	1	0	1
	- moderate	1	1	0	0
	- severe	0	0	0	1
carcinoma, cortical, malignant, primary		0	0	0	1
hematopoiesis, extramedullary	- mild	0	0	1	0
hyperplasia, focal cortical		16	4	10	8
	- minimal	9	3	8	6
	- mild	7	1	2	2
hyperplasia, focal medullary		10	10	11	9
	- minimal	2	7	5	6
	- mild	8	3	6	2
	- moderate	0	0	0	1

( ) - Number observed

MPI Research Study Number 125-141
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H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Incidences of Microscopic Observations - MALE
Terminal

Tissue / Observation	Severity	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
Number of Animals Examined		70	70	70	70
adrenal glands		(70)	(52)	(52)	(70)
hypertrophy, focal cortical	- minimal	2	2	1	1
infarct	- severe	2	0	0	0
leukemia, granulocytic, malignant, multicentric		1	0	1	0
necrosis		1	0	0	2
	- mild	1	0	0	1
	- severe	0	0	0	1
pheochromocytoma, benign, primary		12	9	7	9
pheochromocytoma, malignant, primary		1	2	0	2
vacuolation, diffuse	- mild	0	0	1	0
vacuolation, focal		23	11	10	11
	- minimal	21	10	10	11
	- mild	2	1	0	0
within normal limits		18	23	26	36
aorta		(70)	(50)	(52)	(70)
mineralization		5	1	1	0
	- minimal	0	1	0	0
	- mild	2	0	0	0
	- moderate	2	0	0	0
	- severe	1	0	1	0
sarcoma, histiocytic, malignant, multicentric		0	0	0	1
within normal limits		65	49	51	69

( ) - Number observed

MPI Research Study Number 125-141
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H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Incidences of Microscopic Observations - MALE
Terminal

Tissue / Observation	Severity	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
Number of Animals Examined		70	70	70	70
bile duct, extrahepatic		(1)	(0)	(1)	(0)
calculus/calculi	- moderate	0	0	1	0
dilatation		1	0	1	0
	- mild	1	0	0	0
	- moderate	0	0	1	0
hyperplasia	- mild	0	0	1	0
bone		(1)	(1)	(0)	(0)
osteosarcoma, malignant, primary		1	1	0	0
bone marrow, femur		(70)	(50)	(52)	(70)
hyperplasia, granulocytic		2	1	1	2
	- minimal	1	0	0	1
	- mild	1	1	1	1
hyperplasia, mixed	- mild	0	1	1	1
leukemia, granulocytic, malignant, multicentric		1	0	1	0
leukemia, large granular lymphocyte, malignant, multicentric		0	0	1	0
necrosis	- severe	1	0	0	0
within normal limits		67	48	48	67

( ) - Number observed

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Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Incidences of Microscopic Observations - MALE
Terminal

Tissue / Observation	Severity	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
Number of Animals Examined		70	70	70	70
bone marrow, sternum		(70)	(50)	(52)	(70)
hyperplasia, granulocytic		1	1	1	3
	- minimal	0	0	0	2
	- mild	1	1	1	1
hyperplasia, mixed	- mild	0	1	1	1
leukemia, granulocytic, malignant, multicentric		1	0	1	0
leukemia, large granular lymphocyte, malignant, multicentric		0	0	1	0
sarcoma, histiocytic, malignant, multicentric		0	0	1	0
within normal limits		68	48	48	66
bone marrow, tibia		(1)	(0)	(0)	(0)
leukemia, granulocytic, malignant, multicentric		1	0	0	0
bone, femur		(70)	(51)	(52)	(70)
fibrous osteodystrophy		4	0	1	0
	- minimal	3	0	0	0
	- mild	1	0	0	0
	- moderate	0	0	1	0
hyperostosis	- moderate	1	0	0	0
osteoarthritis/pododermatitis	- moderate	0	1	0	0
osteosarcoma, malignant, primary		1	0	0	0
within normal limits		65	50	51	70

( ) - Number observed

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H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Incidences of Microscopic Observations - MALE
Terminal

Tissue / Observation	Severity	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
Number of Animals Examined		70	70	70	70
bone, sternum		(70)	(50)	(52)	(70)
fibrous osteodystrophy		3	0	1	0
	- minimal	3	0	0	0
	- mild	0	0	1	0
hyperostosis	- moderate	1	0	0	0
lipoma, benign, primary		0	0	0	1
within normal limits		66	50	51	69
brain		(70)	(50)	(52)	(70)
astrocytoma, malignant, primary		1	4	1	0
compression, ventral (pituitary tumor)		22	15	16	17
	- mild	7	7	3	7
	- moderate	15	8	13	10
edema	- moderate	0	0	0	1
hemorrhage	- mild	1	1	0	2
inflammation, embolic	- mild	0	0	0	1
leukemia, large granular lymphocyte, malignant, multicentric		0	0	1	0
mineralization, focal	- minimal	0	0	0	1
necrosis, focal	- moderate	0	0	0	1
schwannoma, malignant, secondary		0	0	0	1
within normal limits		47	31	34	49

( ) - Number observed

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Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Incidences of Microscopic Observations - MALE
Terminal

Tissue / Observation	Severity	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
Number of Animals Examined		70	70	70	70
cavity, abdominal		(1)	(1)	(2)	(3)
fibrosarcoma, malignant, secondary		0	0	0	1
inflammation, acute	- moderate	0	1	0	0
leukemia, granulocytic, malignant, multicentric		1	0	1	0
sarcoma, histiocytic, malignant, multicentric		0	0	1	2
cavity, thoracic		(5)	(0)	(2)	(1)
inflammation, subacute/chronic	- mild	1	0	0	0
leukemia, granulocytic, malignant, multicentric		1	0	1	0
osteosarcoma, malignant, secondary		1	0	0	0
polyarteritis	- moderate	1	0	0	0
sarcoma, histiocytic, malignant, multicentric		1	0	1	1
coagulating glands		(70)	(50)	(53)	(70)
depletion, secretory		4	3	5	5
	- moderate	0	2	2	4
	- severe	4	1	3	1
dilatation	- mild	0	0	1	0
hyperplasia	- mild	0	0	0	1

( ) - Number observed

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Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Incidences of Microscopic Observations - MALE
Terminal

Tissue / Observation	Severity	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
Number of Animals Examined		70	70	70	70
coagulating glands		(70)	(50)	(53)	(70)
inflammation		5	4	3	5
	- minimal	0	0	1	0
	- mild	3	1	0	2
	- moderate	0	2	2	3
	- severe	2	1	0	0
leukemia, granulocytic, malignant, multicentric		1	0	0	0
sarcoma, histiocytic, malignant, multicentric		0	0	1	0
within normal limits		60	43	44	59
epididymides		(70)	(50)	(52)	(70)
granuloma, spermatic	- moderate	0	1	1	0
inflammation, peritoneal	- minimal	1	0	0	1
mesothelioma, malignant, primary		0	1	0	0
oligospermia/germ cell debris, bilateral		6	3	4	4
	- minimal	0	0	1	1
	- mild	1	0	0	0
	- moderate	0	1	0	0
	- severe	5	2	3	3
oligospermia/germ cell debris, unilateral		2	4	2	4
	- mild	0	1	0	0
	- moderate	1	0	0	0
	- severe	1	3	2	4

( ) - Number observed

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H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Incidences of Microscopic Observations - MALE
Terminal

Tissue / Observation	Severity	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
Number of Animals Examined		70	70	70	70
epididymides		(70)	(50)	(52)	(70)
polyarteritis	- mild	0	1	0	0
within normal limits		61	41	46	61
esophagus		(70)	(50)	(52)	(70)
hemorrhage	- mild	0	0	0	1
inflammation	- mild	1	0	0	0
within normal limits		69	50	52	69
eyes		(68)	(49)	(51)	(70)
cataract		3	3	1	3
	- mild	0	0	0	1
	- moderate	2	3	1	2
	- severe	1	0	0	0
hemorrhage		0	1	1	0
	- mild	0	1	0	0
	- moderate	0	0	1	0
inflammation	- moderate	0	0	1	0
inflammation, acute		1	0	2	1
	- minimal	1	0	0	0
	- moderate	0	0	2	1
leukemia, granulocytic, malignant, multicentric		1	0	1	0
melanoma, amelanotic, malignant, primary		1	0	0	0

( ) - Number observed

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Incidences of Microscopic Observations - MALE
Terminal

Tissue / Observation	Severity	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
Number of Animals Examined		70	70	70	70
eyes		(68)	(49)	(51)	(70)
metaplasia, squamous		3	1	1	0
	- minimal	0	1	0	0
	- mild	3	0	1	0
neovascularization, corneal		3	1	0	0
	- minimal	1	0	0	0
	- mild	1	1	0	0
	- moderate	1	0	0	0
sarcoma, histiocytic, malignant, multicentric		0	0	1	0
synechia	- severe	0	0	0	1
within normal limits		61	44	45	66
eyes, optic nerves		(70)	(49)	(51)	(70)
leukemia, granulocytic, malignant, multicentric		0	0	1	0
necrosis	- mild	0	0	0	1
schwannoma, malignant, primary		0	0	0	1
within normal limits		70	49	50	68
eyes, retina		(63)	(42)	(43)	(63)
degeneration/atrophy, retina, unilateral	- mild	0	0	1	1
detachment, retinal	- moderate	0	0	0	1
fold/rosette, retinal	- mild	1	1	1	0
within normal limits		62	41	41	61

( ) - Number observed

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Incidences of Microscopic Observations - MALE
Terminal

Tissue / Observation	Severity	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
Number of Animals Examined		70	70	70	70
foot/feet		(1)	(3)	(1)	(2)
fracture/callus	- no grade	0	0	0	1
inflammation	- moderate	0	2	1	0
osteoarthritis/pododermatitis		1	1	0	1
	- moderate	1	0	0	1
	- severe	0	1	0	0
galt		(70)	(50)	(52)	(70)
leukemia, granulocytic, malignant, multicentric		0	0	1	0
lymphoma, malignant, multicentric		0	1	0	0
within normal limits		70	49	51	70
harderian glands		(68)	(50)	(52)	(70)
hyperplasia, focal		13	11	8	9
	- minimal	13	10	7	7
	- mild	0	1	1	2
leukemia, granulocytic, malignant, multicentric		1	0	1	0
sarcoma, histiocytic, malignant, multicentric		0	0	1	0
within normal limits		54	39	42	61
head		(0)	(0)	(0)	(1)
sarcoma, histiocytic, malignant, multicentric		0	0	0	1

( ) - Number observed

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Incidences of Microscopic Observations - MALE
Terminal

Tissue / Observation	Severity	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
Number of Animals Examined		70	70	70	70
heart		(70)	(50)	(52)	(70)
bacterial colonies	- moderate	0	0	0	1
cardiomyopathy		63	45	46	64
	- minimal	41	27	37	43
	- mild	18	16	7	17
	- moderate	4	2	2	3
	- severe	0	0	0	1
endocarditis, valvular vegetative		0	0	1	1
	- moderate	0	0	1	0
	- severe	0	0	0	1
leukemia, granulocytic, malignant, multicentric		0	0	1	0
mineralization, myofiber		2	0	0	0
	- minimal	1	0	0	0
	- moderate	1	0	0	0
mineralization, vascular	- mild	2	0	1	0
sarcoma, histiocytic, malignant, multicentric		0	0	1	0
schwannoma, malignant, primary		0	1	0	0
thrombus		1	0	0	1
	- mild	1	0	0	0
	- moderate	0	0	0	1
within normal limits		6	4	5	6

( ) - Number observed

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Incidences of Microscopic Observations - MALE
Terminal

Tissue / Observation	Severity	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
Number of Animals Examined		70	70	70	70
hind limb/leg		(0)	(2)	(0)	(0)
inflammation	- moderate	0	2	0	0
joint, tibiofemoral		(70)	(51)	(52)	(70)
degeneration/necrosis, cartilage	- moderate	0	0	0	1
inflammation, subacute/chronic	- mild	0	0	1	0
leukemia, granulocytic, malignant, multicentric		1	0	0	0
osteoarthritis/pododermatitis	- moderate	0	1	0	0
within normal limits		69	50	51	69
kidneys		(70)	(55)	(53)	(70)
adenoma, tubular cell, benign, primary		2	0	0	0
bacterial colonies		0	0	0	2
	- minimal	0	0	0	1
	- mild	0	0	0	1
carcinoma, sebaceous cell, malignant, secondary		0	0	0	1
carcinoma, tubular cell, malignant, primary		0	2	0	0
cyst		5	6	1	2
	- minimal	0	1	0	2
	- mild	4	4	1	0
	- moderate	1	1	0	0

( ) - Number observed

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Incidences of Microscopic Observations - MALE
Terminal

Tissue / Observation	Severity	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
Number of Animals Examined		70	70	70	70
kidneys		(70)	(55)	(53)	(70)
dilatation, tubular		4	0	3	1
	- minimal	1	0	0	0
	- mild	3	0	3	0
	- moderate	0	0	0	1
hemorrhage	- mild	0	0	0	1
hyaline, droplets, increased	- moderate	1	0	2	2
hydronephrosis, bilateral		13	5	8	6
	- minimal	4	2	3	2
	- mild	8	3	5	4
	- moderate	1	0	0	0
hydronephrosis, unilateral		7	4	2	8
	- minimal	4	0	1	4
	- mild	3	4	1	4
hyperplasia, transitional cell		7	5	2	2
	- minimal	3	2	1	1
	- mild	4	3	1	1
hyperplasia, tubular	- mild	1	0	0	0
inflammation, chronic-active	- mild	0	0	1	0
inflammation, embolic		0	0	0	2
	- mild	0	0	0	1
	- moderate	0	0	0	1
leukemia, granulocytic, malignant, multicentric		1	0	1	0

( ) - Number observed

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Incidences of Microscopic Observations - MALE
Terminal

Tissue / Observation	Severity	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
Number of Animals Examined		70	70	70	70
kidneys		(70)	(55)	(53)	(70)
leukemia, large granular lymphocyte, malignant, multicentric		0	0	1	0
mineralization, pelvic		6	2	3	6
	- minimal	6	2	2	5
	- mild	0	0	1	1
mineralization, tubular		6	4	4	8
	- minimal	5	4	2	8
	- mild	0	0	2	0
	- moderate	1	0	0	0
mineralization, vascular	- minimal	1	0	1	0
nephropathy, chronic progressive		68	45	44	67
	- minimal	15	9	10	13
	- mild	27	16	14	38
	- moderate	15	11	16	14
	- severe	11	9	4	2
polyarteritis	- mild	1	0	0	0
pyelitis		11	8	3	3
	- minimal	8	5	3	2
	- mild	3	3	0	1
pyelonephritis, bilateral	- mild	0	1	0	0
sarcoma, histiocytic, malignant, multicentric		0	0	1	2

( ) - Number observed

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Incidences of Microscopic Observations - MALE
Terminal

Tissue / Observation	Severity	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
Number of Animals Examined		70	70	70	70
kidneys		(70)	(55)	(53)	(70)
thrombus		2	1	1	0
	- mild	2	1	0	0
	- moderate	0	0	1	0
within normal limits		0	6	6	2
lacrimal glands, exorbital		(69)	(49)	(52)	(70)
atrophy		0	1	0	1
	- minimal	0	1	0	0
	- mild	0	0	0	1
depletion, secretory	- moderate	0	1	0	0
leukemia, granulocytic, malignant, multicentric		1	0	1	0
sarcoma, histiocytic, malignant, multicentric		0	0	1	0
within normal limits		68	47	50	69
large intestine, cecum		(70)	(50)	(52)	(70)
edema	- moderate	0	0	0	1
inflammation	- mild	0	0	1	0
polyarteritis	- minimal	0	0	0	1
within normal limits		70	50	51	68
large intestine, colon		(70)	(50)	(52)	(70)
within normal limits		70	50	52	70

( ) - Number observed

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Incidences of Microscopic Observations - MALE
Terminal

Tissue / Observation	Severity	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
Number of Animals Examined		70	70	70	70
large intestine, rectum		(70)	(50)	(52)	(70)
inflammation, peritoneal	- mild	0	1	0	0
sarcoma, histiocytic, malignant, multicentric		0	0	1	1
within normal limits		70	49	51	69
larynx		(70)	(49)	(52)	(70)
erosion/ulcer	- mild	0	0	0	1
exudate, luminal		0	1	1	1
	- minimal	0	1	1	0
	- mild	0	0	0	1
foreign material		0	2	0	0
	- mild	0	1	0	0
	- moderate	0	1	0	0
inflammation		0	1	0	2
	- minimal	0	1	0	1
	- mild	0	0	0	1
leukemia, granulocytic, malignant, multicentric		1	0	1	0
mucus increased		0	0	2	2
	- minimal	0	0	1	0
	- mild	0	0	1	2
within normal limits		69	47	49	66

( ) - Number observed

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Incidences of Microscopic Observations - MALE
Terminal

Tissue / Observation	Severity	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
Number of Animals Examined		70	70	70	70
liver		(70)	(70)	(70)	(70)
adenoma, hepatocellular, benign, primary		1	2	1	1
angiectasis	- minimal	2	0	1	1
carcinoma, hepatocellular, malignant, primary		1	0	0	2
congestion	- severe	0	0	0	1
cyst, biliary, multiloculated	- mild	0	1	0	0
cyst, biliary, simple	- minimal	0	0	0	1
degeneration, cystic, focal		24	24	19	42
	- minimal	18	20	18	27
	- mild	5	4	1	15
	- moderate	1	0	0	0
fibrosis		0	2	0	2
	- minimal	0	2	0	1
	- mild	0	0	0	1
focus of cellular alteration, basophilic		6	5	6	13
	- minimal	6	5	6	10
	- mild	0	0	0	3
focus of cellular alteration, clear		2	1	2	3
	- minimal	2	1	2	2
	- mild	0	0	0	1

( ) - Number observed

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Incidences of Microscopic Observations - MALE
Terminal

Tissue / Observation	Severity	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
Number of Animals Examined		70	70	70	70
liver		(70)	(70)	(70)	(70)
focus of cellular alteration, eosinophilic		15	18	6	15
	- minimal	11	18	6	10
	- mild	4	0	0	5
hematopoiesis, extramedullary	- minimal	19	28	24	19
hyperplasia, bile duct		40	33	32	34
	- minimal	35	30	29	33
	- mild	4	3	3	1
	- moderate	1	0	0	0
hyperplasia, hepatocellular, regenerative	- mild	0	0	0	1
hypertrophy, hepatocyte, centrilobular	- minimal	0	0	0	7
infarct	- severe	0	1	0	0
infiltration, mononuclear cell	- minimal	36	28	20	25
inflammation, acute	- minimal	1	0	0	0
leukemia, granulocytic, malignant, multicentric		1	0	1	0
leukemia, large granular lymphocyte, malignant, multicentric		0	0	1	0
leukocytosis, sinusoidal	- minimal	0	1	1	0
macrophages, pigmented	- minimal	0	1	0	0
necrosis, focal		6	3	4	9
	- minimal	5	2	3	6
	- mild	1	0	1	3
	- severe	0	1	0	0

( ) - Number observed

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Incidences of Microscopic Observations - MALE
Terminal

Tissue / Observation	Severity	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
Number of Animals Examined		70	70	70	70
liver		(70)	(70)	(70)	(70)
necrosis, hepatocytes, centrilobular		1	0	1	5
	- minimal	0	0	0	1
	- moderate	1	0	0	1
	- severe	0	0	1	3
osteosarcoma, malignant, secondary		1	0	0	0
sarcoma, histiocytic, malignant, multicentric		0	0	0	2
vacuolation, centrilobular		4	6	2	2
	- minimal	4	4	1	2
	- mild	0	1	1	0
	- moderate	0	1	0	0
vacuolation, diffuse		3	1	1	0
	- minimal	2	0	0	0
	- mild	0	1	1	0
	- moderate	1	0	0	0
vacuolation, focal		9	7	5	2
	- minimal	8	7	5	2
	- moderate	1	0	0	0
vacuolation, median cleft		1	0	2	3
	- minimal	0	0	0	1
	- mild	1	0	2	2

( ) - Number observed

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Incidences of Microscopic Observations - MALE
Terminal

Tissue / Observation	Severity	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
Number of Animals Examined		70	70	70	70
liver		(70)	(70)	(70)	(70)
vacuolation, midzonal		1	2	0	0
	- minimal	1	1	0	0
	- mild	0	1	0	0
vacuolation, periportal		18	16	16	7
	- minimal	13	9	11	6
	- mild	5	4	5	1
	- moderate	0	1	0	0
	- severe	0	2	0	0
within normal limits		7	6	6	5
lung		(70)	(50)	(53)	(70)
adenocarcinoma (primary site unknown), malignant, primary		0	1	0	0
bacterial colonies		3	6	6	3
	- minimal	2	2	4	2
	- mild	1	4	2	1
carcinoma, c-cell, malignant, secondary		1	0	0	0
carcinoma, cortical, malignant, secondary		0	0	0	1
carcinoma, sebaceous cell (primary site unknown), malignant, primary		0	0	0	1
crystals, hemoglobin		0	0	1	1
	- minimal	0	0	0	1
	- mild	0	0	1	0
edema	- mild	1	0	0	0

( ) - Number observed

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Incidences of Microscopic Observations - MALE
Terminal

Tissue / Observation	Severity	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
Number of Animals Examined		70	70	70	70
lung		(70)	(50)	(53)	(70)
foreign material	- minimal	0	1	0	1
granuloma	- minimal	0	1	0	2
hemangiosarcoma, malignant, secondary		0	1	0	0
hemorrhage		1	0	3	1
	- minimal	1	0	1	1
	- mild	0	0	2	0
histiocytosis, alveolar	- minimal	23	15	10	26
hyperplasia, bronchiolar-alveolar	- mild	0	0	1	0
hyperplasia, type II cell	- mild	0	1	0	0
hypertrophy/hyperplasia, bronchiolar/bronchial	- mild	0	0	1	0
inflammation, acute		1	0	0	3
	- minimal	1	0	0	2
	- mild	0	0	0	1
inflammation, perivascular	- mild	0	0	1	0
inflammation, subacute/chronic		2	1	3	1
	- minimal	2	1	2	1
	- mild	0	0	1	0
leukemia, granulocytic, malignant, multicentric		1	0	1	0
leukemia, large granular lymphocyte, malignant, multicentric		0	0	1	0
leukocytosis, vascular	- mild	0	0	1	0
macrophages, alveolar	- mild	1	1	1	0
macrophages, pigmented alveolar	- minimal	1	2	0	0

( ) - Number observed

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Incidences of Microscopic Observations - MALE
Terminal

Tissue / Observation	Severity	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
Number of Animals Examined		70	70	70	70
lung		(70)	(50)	(53)	(70)
metaplasia, osseous	- minimal	0	1	0	0
mucus increased	- mild	0	0	1	0
necrosis	- mild	0	0	0	1
osteosarcoma, malignant, secondary		1	0	0	0
pneumonitis, uremic		3	0	1	0
	- minimal	3	0	0	0
	- moderate	0	0	1	0
sarcoma, histiocytic, malignant, multicentric		1	0	1	3
thrombus	- moderate	1	0	0	0
within normal limits		33	22	26	31
lymph node, axillary		(12)	(5)	(6)	(8)
erythrocytosis/erythrophagocytosis, sinus		1	1	0	0
	- minimal	1	0	0	0
	- mild	0	1	0	0
histiocytosis, sinus	- mild	1	0	0	0
hyperplasia, lymphoid, generalized	- mild	0	0	0	1
leukemia, granulocytic, malignant, multicentric		1	0	0	0
sarcoma, histiocytic, malignant, multicentric		0	0	0	1
within normal limits		10	4	6	6

( ) - Number observed

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Incidences of Microscopic Observations - MALE
Terminal

Tissue / Observation	Severity	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
Number of Animals Examined		70	70	70	70
lymph node, hepatic		(3)	(1)	(1)	(2)
leukemia, granulocytic, malignant, multicentric		1	0	0	0
leukemia, large granular lymphocyte, malignant, multicentric		0	0	1	0
within normal limits		2	1	0	2
lymph node, iliac		(0)	(2)	(2)	(1)
dilatation, sinus		0	2	1	1
	- minimal	0	0	1	0
	- mild	0	1	0	1
	- moderate	0	1	0	0
hyperplasia, lymphocyte/plasmacyte, medulla	- mild	0	0	1	1
leukemia, granulocytic, malignant, multicentric		0	0	1	0
lymph node, inguinal		(1)	(5)	(5)	(0)
hyperplasia, lymphocyte/plasmacyte, medulla	- mild	0	1	0	0
within normal limits		1	4	5	0
lymph node, mandibular		(70)	(49)	(53)	(69)
dilatation, sinus		4	2	4	2
	- minimal	2	1	3	2
	- mild	2	1	1	0

( ) - Number observed

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Incidences of Microscopic Observations - MALE
Terminal

Tissue / Observation	Severity	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
Number of Animals Examined		70	70	70	70
lymph node, mandibular		(70)	(49)	(53)	(69)
erythrocytosis/erythrophagocytosis, sinus		7	6	3	11
	- minimal	7	5	1	10
	- mild	0	1	2	1
hemorrhage	- moderate	1	0	0	0
hyperplasia, lymphocyte/plasmacyte, medulla	- mild	1	1	0	0
leukemia, granulocytic, malignant, multicentric		1	0	1	0
leukemia, large granular lymphocyte, malignant, multicentric		0	0	1	0
lymphoma, malignant, multicentric		0	0	0	1
osteosarcoma, malignant, secondary		1	0	0	0
sarcoma, histiocytic, malignant, multicentric		0	0	1	0
within normal limits		57	41	43	55
lymph node, mediastinal		(3)	(1)	(3)	(3)
dilatation, sinus	- moderate	0	1	1	0
leukemia, granulocytic, malignant, multicentric		0	0	1	0
leukemia, large granular lymphocyte, malignant, multicentric		0	0	1	0
lymphoma, malignant, multicentric		0	0	0	1
sarcoma, histiocytic, malignant, multicentric		0	0	1	1
within normal limits		3	0	0	1
lymph node, mesenteric		(70)	(51)	(54)	(70)
depletion, lymphoid, generalized	- moderate	0	0	0	1

( ) - Number observed

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Incidences of Microscopic Observations - MALE
Terminal

Tissue / Observation	Severity	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
Number of Animals Examined		70	70	70	70
lymph node, mesenteric		(70)	(51)	(54)	(70)
dilatation, sinus		3	2	1	2
	- minimal	2	0	0	2
	- mild	1	2	0	0
	- moderate	0	0	1	0
erythrocytosis/erythrophagocytosis, sinus		5	1	1	1
	- minimal	2	0	0	0
	- mild	3	1	1	1
hemangiosarcoma, malignant, primary		1	0	2	0
inflammation, granulomatous	- minimal	0	1	0	0
leukemia, granulocytic, malignant, multicentric		1	0	1	0
leukemia, large granular lymphocyte, malignant, multicentric		0	0	1	0
lymphoma, malignant, multicentric		0	1	0	1
sarcoma, histiocytic, malignant, multicentric		0	0	1	0
within normal limits		60	46	47	67
lymph node, popliteal		(0)	(0)	(1)	(0)
within normal limits		0	0	1	0
lymph node, renal		(0)	(2)	(0)	(0)
erythrocytosis/erythrophagocytosis, sinus	- mild	0	1	0	0
within normal limits		0	1	0	0

( ) - Number observed

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Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Incidences of Microscopic Observations - MALE
Terminal

Tissue / Observation	Severity	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
Number of Animals Examined		70	70	70	70
mammary gland		(4)	(5)	(3)	(4)
adenocarcinoma, malignant, primary		1	0	0	0
adenoma, benign, primary		0	1	0	0
dilatation, gland/lumen	- mild	2	2	2	1
fibroadenoma, benign, primary		2	1	1	3
hyperplasia, lobular	- mild	0	1	0	0
mesentery/peritoneum		(4)	(1)	(0)	(1)
necrosis, fat	- mild	1	1	0	1
polyarteritis		3	0	0	0
	- minimal	1	0	0	0
	- mild	1	0	0	0
	- moderate	1	0	0	0
multicentric neoplasm		(2)	(1)	(3)	(4)
leukemia, granulocytic, malignant, multicentric		1	0	1	0
leukemia, large granular lymphocyte, malignant, multicentric		0	0	1	0
lymphoma, malignant, multicentric		0	1	0	1
sarcoma, histiocytic, malignant, multicentric		1	0	1	3

( ) - Number observed

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Incidences of Microscopic Observations - MALE
Terminal

Tissue / Observation	Severity	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
Number of Animals Examined		70	70	70	70
nerve, sciatic		(70)	(50)	(52)	(70)
degeneration, axonal/myelin		49	31	22	42
	- minimal	43	28	21	40
	- mild	4	2	1	1
	- moderate	2	1	0	1
within normal limits		21	19	30	28
nose, level a		(70)	(50)	(52)	(70)
adenocarcinoma, malignant, primary		0	0	0	1
exudate, nasal passage		9	0	2	5
	- minimal	3	0	1	4
	- mild	4	0	0	0
	- moderate	2	0	1	1
fibrous osteodystrophy		1	0	1	0
	- mild	1	0	0	0
	- moderate	0	0	1	0
foreign material	- minimal	1	0	2	0
fungus/yeast		4	0	1	2
	- mild	2	0	0	1
	- moderate	2	0	1	1

( ) - Number observed

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Incidences of Microscopic Observations - MALE
Terminal

Tissue / Observation	Severity	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
Number of Animals Examined		70	70	70	70
nose, level a		(70)	(50)	(52)	(70)
inflammation		7	2	1	4
	- minimal	5	2	0	3
	- mild	2	0	0	1
	- moderate	0	0	1	0
leukemia, granulocytic, malignant, multicentric		1	0	0	0
metaplasia, squamous		2	0	0	1
	- minimal	2	0	0	0
	- mild	0	0	0	1
sarcoma, histiocytic, malignant, multicentric		0	0	1	0
within normal limits		59	48	47	64
nose, level b		(70)	(50)	(52)	(70)
erosion/ulcer	- moderate	1	0	0	0
exudate, nasal passage		13	1	4	3
	- minimal	5	1	2	1
	- mild	5	0	2	0
	- moderate	3	0	0	2
fibrous osteodystrophy		2	0	1	0
	- minimal	1	0	0	0
	- mild	1	0	0	0
	- moderate	0	0	1	0

( ) - Number observed

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Incidences of Microscopic Observations - MALE
Terminal

Tissue / Observation	Severity	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
Number of Animals Examined		70	70	70	70
nose, level b		(70)	(50)	(52)	(70)
foreign material		2	1	1	0
	- minimal	2	0	0	0
	- mild	0	1	0	0
	- moderate	0	0	1	0
fungus/yeast		7	0	3	2
	- mild	1	0	1	0
	- moderate	5	0	1	1
	- severe	1	0	1	1
inflammation		9	0	1	2
	- minimal	3	0	0	0
	- mild	6	0	1	1
	- moderate	0	0	0	1
inflammation, acute	- minimal	0	0	1	0
leukemia, granulocytic, malignant, multicentric		1	0	0	0
metaplasia, squamous		4	0	1	1
	- minimal	4	0	1	0
	- moderate	0	0	0	1
odontodysplasia	- moderate	1	0	0	0
sarcoma, histiocytic, malignant, multicentric		0	0	1	0
within normal limits		52	48	45	67

( ) - Number observed

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Incidences of Microscopic Observations - MALE
Terminal

Tissue / Observation	Severity	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
Number of Animals Examined		70	70	70	70
nose, level c		(70)	(50)	(52)	(70)
erosion/ulcer		3	0	1	0
	- mild	2	0	1	0
	- moderate	1	0	0	0
exudate, nasal passage		8	1	4	3
	- minimal	2	1	1	1
	- mild	4	0	2	2
	- moderate	2	0	1	0
fibrous osteodystrophy		3	0	1	0
	- minimal	1	0	0	0
	- mild	2	0	0	0
	- moderate	0	0	1	0
foreign material		1	1	3	1
	- minimal	1	1	2	1
	- mild	0	0	1	0
fungus/yeast		5	0	2	1
	- mild	1	0	0	0
	- moderate	2	0	1	0
	- severe	2	0	1	1
inflammation		6	0	1	1
	- minimal	1	0	0	0
	- mild	5	0	1	1
inflammation, acute	- minimal	0	0	1	0

( ) - Number observed

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Incidences of Microscopic Observations - MALE
Terminal

Tissue / Observation	Severity	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
Number of Animals Examined		70	70	70	70
nose, level c		(70)	(50)	(52)	(70)
leukemia, granulocytic, malignant, multicentric		1	0	0	0
metaplasia, squamous		7	0	2	2
	- minimal	0	0	0	1
	- mild	5	0	2	0
	- moderate	2	0	0	1
sarcoma, histiocytic, malignant, multicentric		0	0	1	0
within normal limits		58	49	45	67
nose, level d		(70)	(50)	(52)	(70)
erosion/ulcer		1	0	1	1
	- mild	0	0	0	1
	- moderate	1	0	1	0
exudate, nasal passage		5	1	3	0
	- minimal	2	0	1	0
	- mild	2	1	2	0
	- moderate	1	0	0	0
fibrous osteodystrophy		3	0	1	0
	- minimal	1	0	0	0
	- mild	2	0	0	0
	- moderate	0	0	1	0

( ) - Number observed

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Incidences of Microscopic Observations - MALE
Terminal

Tissue / Observation	Severity	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
Number of Animals Examined		70	70	70	70
nose, level d		(70)	(50)	(52)	(70)
foreign material		0	1	3	0
	- minimal	0	1	2	0
	- mild	0	0	1	0
fungus/yeast	- severe	1	0	0	0
inflammation	- minimal	2	0	2	1
inflammation, acute	- mild	0	0	1	0
leukemia, granulocytic, malignant, multicentric		1	0	0	0
leukemia, large granular lymphocyte, malignant, multicentric		0	0	1	0
metaplasia, squamous		3	0	1	1
	- mild	1	0	1	1
	- moderate	2	0	0	0
sarcoma, histiocytic, malignant, multicentric		0	0	1	0
within normal limits		62	48	44	69
pancreas		(70)	(70)	(70)	(70)
adenoma, acinar cell, benign, primary		0	1	0	3
adenoma, islet cell, benign, primary		9	9	7	7
atrophy, acinar		17	17	17	12
	- minimal	13	16	13	10
	- mild	4	1	3	2
	- severe	0	0	1	0
carcinoma, acinar cell, malignant, primary		0	0	0	2

( ) - Number observed

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Incidences of Microscopic Observations - MALE
Terminal

Tissue / Observation	Severity	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
Number of Animals Examined		70	70	70	70
pancreas		(70)	(70)	(70)	(70)
carcinoma, islet cell, malignant, primary		1	4	1	2
fibrosis		21	14	21	18
	- minimal	21	14	20	18
	- mild	0	0	1	0
hyperplasia, acinar cell, focal		16	18	7	21
	- minimal	6	5	1	8
	- mild	6	10	5	11
	- moderate	4	3	1	2
hyperplasia, islet cell		2	0	2	3
	- minimal	1	0	1	1
	- mild	1	0	1	2
inflammation, acute	- mild	0	1	0	0
leukemia, granulocytic, malignant, multicentric		1	0	1	0
mineralization, vascular	- mild	0	0	1	0
polyarteritis		2	2	2	0
	- minimal	0	0	1	0
	- mild	1	0	0	0
	- moderate	1	2	1	0
sarcoma, histiocytic, malignant, multicentric		0	0	1	2
within normal limits		28	26	25	24

( ) - Number observed

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Incidences of Microscopic Observations - MALE
Terminal

Tissue / Observation	Severity	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
Number of Animals Examined		70	70	70	70
parathyroid glands		(64)	(43)	(46)	(60)
adenoma, benign, primary		1	2	0	1
carcinoma, c-cell, malignant, secondary		0	0	0	1
hyperplasia, diffuse		1	0	2	0
	- minimal	0	0	1	0
	- mild	1	0	0	0
	- moderate	0	0	1	0
hyperplasia, focal		5	1	1	6
	- minimal	2	1	1	3
	- mild	3	0	0	3
within normal limits		57	40	43	52
pharynx		(70)	(49)	(52)	(69)
hemorrhage	- moderate	0	0	0	1
hyperplasia, squamous epithelium	- mild	0	0	0	1
inflammation		0	0	0	2
	- minimal	0	0	0	1
	- moderate	0	0	0	1
papilloma, squamous cell, benign, primary		0	0	0	1
within normal limits		70	49	52	66
pituitary gland		(70)	(52)	(60)	(70)
adenoma, pars distalis, benign, primary		51	31	42	46

( ) - Number observed

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Incidences of Microscopic Observations - MALE
Terminal

Tissue / Observation	Severity	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
Number of Animals Examined		70	70	70	70
pituitary gland		(70)	(52)	(60)	(70)
cyst		4	4	0	1
	- minimal	1	0	0	0
	- mild	1	4	0	1
	- moderate	2	0	0	0
fibrosis	- moderate	0	0	1	0
hyperplasia, craniopharyngeal		0	0	0	2
	- minimal	0	0	0	1
	- mild	0	0	0	1
hyperplasia, focal, pars distalis		6	4	3	3
	- minimal	2	2	2	1
	- mild	2	2	1	2
	- moderate	2	0	0	0
macrophages, pigmented	- mild	0	0	1	0
schwannoma, malignant, secondary		0	0	0	1
within normal limits		9	14	14	19
preputial glands		(0)	(1)	(0)	(1)
carcinoma, squamous cell, malignant, primary		0	1	0	0
dilatation/inflammation	- mild	0	0	0	1
hyperplasia, squamous cell	- moderate	0	0	0	1

( ) - Number observed

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Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Incidences of Microscopic Observations - MALE
Terminal

Tissue / Observation	Severity	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
Number of Animals Examined		70	70	70	70
prostate gland		(70)	(51)	(53)	(70)
abscess	- severe	0	0	1	0
adenoma, benign, primary		1	0	0	0
inflammation, acute		4	4	4	2
	- minimal	1	1	2	0
	- mild	0	0	0	1
	- moderate	3	1	1	1
	- severe	0	2	1	0
inflammation, chronic-active		12	2	1	10
	- minimal	3	0	0	1
	- mild	2	0	0	5
	- moderate	3	1	1	3
	- severe	4	1	0	1
inflammation, subacute/chronic		3	2	1	3
	- minimal	0	0	0	1
	- mild	1	0	1	1
	- moderate	1	2	0	0
	- severe	1	0	0	1
leukemia, granulocytic, malignant, multicentric		1	0	1	0
sarcoma, histiocytic, malignant, multicentric		0	0	1	0
within normal limits		49	43	44	55

( ) - Number observed

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Incidences of Microscopic Observations - MALE
Terminal

Tissue / Observation	Severity	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
Number of Animals Examined		70	70	70	70
salivary gland, mandibular		(70)	(49)	(52)	(69)
depletion, secretory	- severe	1	0	0	0
fibrosis	- mild	0	0	0	1
mineralization, vascular	- minimal	0	0	1	0
sarcoma, histiocytic, malignant, multicentric		0	0	1	0
within normal limits		69	49	50	68
salivary gland, parotid		(70)	(49)	(52)	(70)
atrophy	- minimal	1	2	0	0
leukemia, granulocytic, malignant, multicentric		0	0	1	0
sarcoma, histiocytic, malignant, multicentric		0	0	1	0
within normal limits		69	47	50	70
salivary gland, sublingual		(69)	(49)	(52)	(68)
depletion, secretory	- severe	1	0	0	0
within normal limits		68	49	52	68
seminal vesicles		(70)	(50)	(53)	(70)
depletion, secretory		5	3	5	6
	- moderate	0	2	2	5
	- severe	5	1	3	1

( ) - Number observed

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Incidences of Microscopic Observations - MALE
Terminal

Tissue / Observation	Severity	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
Number of Animals Examined		70	70	70	70
seminal vesicles		(70)	(50)	(53)	(70)
dilatation		1	0	1	2
	- mild	1	0	1	1
	- moderate	0	0	0	1
inflammation		8	5	2	3
	- minimal	0	2	2	0
	- mild	6	1	0	2
	- moderate	2	1	0	1
	- severe	0	1	0	0
sarcoma, histiocytic, malignant, multicentric		0	0	1	1
within normal limits		57	42	45	59
skeletal muscle		(0)	(0)	(1)	(0)
leukemia, granulocytic, malignant, multicentric		0	0	1	0
skeletal muscle, biceps femoris		(70)	(50)	(52)	(70)
atrophy	- mild	2	1	1	0
degeneration/necrosis, myofiber		18	8	5	20
	- minimal	14	5	3	18
	- mild	4	3	2	2
degeneration/regeneration, myofiber	- minimal	2	1	0	1
sarcoma, histiocytic, malignant, multicentric		0	0	1	1
within normal limits		49	41	46	49

( ) - Number observed

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Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Incidences of Microscopic Observations - MALE
Terminal

Tissue / Observation	Severity	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
Number of Animals Examined		70	70	70	70
skin		(70)	(58)	(58)	(70)
abscess	- mild	1	0	0	0
adenoma, basal cell, benign, primary		0	0	1	1
adenoma, sebaceous cell, benign, primary		0	2	1	0
alopecia/hypotrichosis	- mild	1	1	0	0
carcinoma, squamous cell, malignant, primary		0	3	2	0
crust, serocellular		0	2	0	0
	- mild	0	1	0	0
	- moderate	0	1	0	0
cyst, keratin	- mild	0	0	1	0
erosion/ulcer		1	2	2	0
	- mild	0	1	1	0
	- moderate	1	1	1	0
hyperkeratosis	- mild	1	0	0	0
hyperplasia, epidermal		1	2	1	1
	- mild	1	1	1	1
	- moderate	0	1	0	0
inflammation	- mild	0	1	0	0
keratoacanthoma, benign, primary		3	6	5	3
papilloma, squamous cell, benign, primary		0	1	0	2
sarcoma, histiocytic, malignant, multicentric		0	0	1	0
within normal limits		64	44	45	64

( ) - Number observed

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Incidences of Microscopic Observations - MALE
Terminal

Tissue / Observation	Severity	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
Number of Animals Examined		70	70	70	70
skin, subcutis		(9)	(5)	(13)	(9)
abscess		1	0	1	0
	- moderate	0	0	1	0
	- severe	1	0	0	0
fibroma, benign, primary		4	1	4	5
fibrosarcoma, malignant, primary		1	1	4	1
hemangiosarcoma, malignant, primary		0	1	0	0
leukemia, granulocytic, malignant, multicentric		0	0	1	0
lipoma, benign, primary		3	2	2	1
osteosarcoma, malignant, secondary		1	0	0	0
sarcoma, histiocytic, malignant, multicentric		0	0	1	2
small intestine, duodenum		(70)	(50)	(52)	(70)
hyperplasia, mucosal	- mild	0	1	0	0
within normal limits		70	49	52	70
small intestine, ileum		(70)	(51)	(53)	(70)
adenocarcinoma, malignant, primary		0	0	1	0
dilatation, gland/lumen	- mild	1	0	0	1
diverticulum	- mild	1	0	0	0
lymphoma, malignant, multicentric		0	1	0	0
within normal limits		68	50	52	69

( ) - Number observed

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Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Incidences of Microscopic Observations - MALE
Terminal

Tissue / Observation	Severity	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
Number of Animals Examined		70	70	70	70
small intestine, jejunum		(70)	(51)	(52)	(70)
adenocarcinoma, malignant, primary		0	2	0	0
dilatation, gland/lumen		1	1	0	0
	- mild	1	0	0	0
	- moderate	0	1	0	0
erosion/ulcer	- severe	0	1	0	0
lymphangiectasis	- mild	0	1	0	0
within normal limits		69	47	52	70
spinal cord, cervical		(70)	(50)	(52)	(70)
within normal limits		70	50	52	70
spinal cord, lumbar		(70)	(50)	(52)	(70)
astrocytoma, malignant, primary		1	1	0	0
within normal limits		69	49	52	70
spinal cord, thoracic		(70)	(50)	(52)	(70)
astrocytoma, malignant, primary		0	0	0	1
degeneration, axonal/myelin	- mild	0	0	0	1
within normal limits		70	50	52	68

( ) - Number observed

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Incidences of Microscopic Observations - MALE
Terminal

Tissue / Observation	Severity	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
Number of Animals Examined		70	70	70	70
spleen		(70)	(50)	(52)	(70)
cyst, capsule	- mild	1	0	0	0
depletion, lymphoid, generalized	- moderate	0	0	0	1
hemangiosarcoma, malignant, primary		0	1	0	0
hematopoiesis, extramedullary, increased		26	15	16	23
	- minimal	24	14	13	21
	- mild	2	1	2	1
	- moderate	0	0	1	1
hyperplasia, reactive red pulp/stromal	- mild	0	0	0	1
inflammation, peritoneal	- mild	0	1	0	0
leukemia, granulocytic, malignant, multicentric		1	0	1	0
leukemia, large granular lymphocyte, malignant, multicentric		0	0	1	0
within normal limits		42	33	34	45
stomach, glandular		(70)	(50)	(53)	(70)
erosion/ulcer		0	2	3	1
	- minimal	0	0	2	0
	- mild	0	1	1	1
	- moderate	0	1	0	0
gastropathy, uremic		4	1	2	0
	- minimal	0	1	1	0
	- mild	3	0	0	0
	- moderate	1	0	1	0

( ) - Number observed

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Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Incidences of Microscopic Observations - MALE
Terminal

Tissue / Observation	Severity	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
Number of Animals Examined		70	70	70	70
stomach, glandular		(70)	(50)	(53)	(70)
hyperplasia, mucosal	- mild	0	1	0	0
inflammation	- minimal	0	0	1	0
leukemia, granulocytic, malignant, multicentric		0	0	1	0
sarcoma, histiocytic, malignant, multicentric		0	0	1	2
within normal limits		66	47	46	67
stomach, nonglandular		(70)	(51)	(52)	(70)
cyst, keratin	- mild	0	0	0	1
erosion/ulcer		5	4	5	5
	- minimal	1	0	1	0
	- mild	2	1	1	0
	- moderate	1	1	3	3
	- severe	1	2	0	2
gastropathy, uremic	- mild	0	0	1	0
hyperplasia, epithelial, limiting ridge	- mild	0	1	0	0
hyperplasia, epithelial, nonglandular		6	3	4	8
	- mild	1	1	0	2
	- moderate	5	2	4	6
inflammation		7	3	5	7
	- minimal	1	0	1	2
	- mild	4	3	4	3
	- moderate	2	0	0	2

( ) - Number observed

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Incidences of Microscopic Observations - MALE
Terminal

Tissue / Observation	Severity	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
Number of Animals Examined		70	70	70	70
stomach, nonglandular		(70)	(51)	(52)	(70)
papilloma, squamous cell, benign, primary		1	0	0	0
sarcoma, histiocytic, malignant, multicentric		0	0	0	1
within normal limits		62	43	44	59
tail		(0)	(1)	(0)	(0)
erosion/ulcer	- severe	0	1	0	0
testes		(70)	(70)	(70)	(70)
adenoma, interstitial cell, benign, primary		4	4	1	8
degeneration/atrophy, seminiferous tubules, bilateral		7	4	5	3
	- minimal	1	0	0	1
	- mild	0	2	1	0
	- moderate	1	1	1	0
	- severe	5	1	3	2
degeneration/atrophy, seminiferous tubules, unilateral		3	3	1	4
	- minimal	1	0	0	1
	- mild	0	0	0	1
	- moderate	1	1	0	1
	- severe	1	2	1	1
dilatation, seminiferous tubules, bilateral	- minimal	0	1	0	0
dilatation, seminiferous tubules, unilateral	- mild	0	0	2	0

( ) - Number observed

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Incidences of Microscopic Observations - MALE
Terminal

Tissue / Observation	Severity	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
Number of Animals Examined		70	70	70	70
testes		(70)	(70)	(70)	(70)
edema		1	1	1	0
	- moderate	1	1	0	0
	- severe	0	0	1	0
granuloma, spermatic	- moderate	0	0	1	0
hemangioma, benign, primary		0	1	0	0
hyperplasia, interstitial cell		7	7	3	15
	- minimal	7	7	3	14
	- moderate	0	0	0	1
inflammation, peritoneal	- minimal	0	0	0	1
mesothelioma, malignant, secondary		0	1	0	0
polyarteritis		6	5	7	1
	- minimal	3	2	4	0
	- mild	3	3	3	1
within normal limits		48	50	52	46
thymus		(69)	(50)	(52)	(68)
depletion, lymphoid, generalized		67	46	49	68
	- mild	3	2	0	0
	- moderate	16	21	31	30
	- severe	48	23	18	38
hyperplasia, epithelial cell	- minimal	0	1	0	0
hyperplasia, lymphoid, medulla	- minimal	0	1	0	0

( ) - Number observed

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Incidences of Microscopic Observations - MALE
Terminal

Tissue / Observation	Severity	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
Number of Animals Examined		70	70	70	70
thymus		(69)	(50)	(52)	(68)
leukemia, granulocytic, malignant, multicentric		0	0	1	0
lymphoma, malignant, multicentric		0	0	0	1
sarcoma, histiocytic, malignant, multicentric		0	0	1	0
thymoma, malignant, primary		1	0	0	0
within normal limits		1	4	2	0
thyroid gland		(70)	(51)	(53)	(70)
adenoma, c-cell, benign, primary		7	6	5	4
adenoma, follicular cell, benign, primary		3	1	2	0
carcinoma, c-cell, malignant, primary		1	2	1	1
carcinoma, follicular cell, malignant, primary		0	0	1	0
cyst, follicular	- mild	0	2	1	0
hyperplasia, c-cell, focal		9	3	3	3
	- minimal	1	2	1	2
	- mild	7	0	2	1
	- moderate	1	1	0	0
hyperplasia, follicular cell	- mild	1	0	0	0
hypertrophy/hyperplasia, follicular cell		0	1	0	1
	- mild	0	0	0	1
	- moderate	0	1	0	0
inflammation, subacute/chronic	- mild	0	1	0	0
leukemia, granulocytic, malignant, multicentric		0	0	1	0

( ) - Number observed

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Incidences of Microscopic Observations - MALE
Terminal

Tissue / Observation	Severity	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
Number of Animals Examined		70	70	70	70
thyroid gland		(70)	(51)	(53)	(70)
sarcoma, histiocytic, malignant, multicentric		0	0	0	1
within normal limits		52	37	42	61
tongue		(70)	(69)	(70)	(69)
hyperplasia, squamous cell		0	0	0	2
	- minimal	0	0	0	1
	- moderate	0	0	0	1
inflammation, subacute/chronic		1	0	0	2
	- minimal	1	0	0	1
	- mild	0	0	0	1
mineralization, vascular	- minimal	0	0	1	0
sarcoma, histiocytic, malignant, multicentric		0	0	0	1
within normal limits		69	69	69	66
trachea		(70)	(50)	(52)	(70)
bacterial colonies	- minimal	0	0	1	0
exudate, luminal	- minimal	0	0	0	1
inflammation, acute	- minimal	1	0	0	0
leukemia, granulocytic, malignant, multicentric		0	0	1	0
within normal limits		69	50	50	69

( ) - Number observed

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Incidences of Microscopic Observations - MALE
Terminal

Tissue / Observation	Severity	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
Number of Animals Examined		70	70	70	70
ureters		(70)	(51)	(52)	(70)
crystals, hemoglobin	- mild	1	0	0	0
dilatation		5	2	5	1
	- mild	4	2	3	1
	- moderate	1	0	2	0
hemorrhage	- mild	0	0	1	0
inflammation	- minimal	0	0	0	1
within normal limits		65	49	47	69
urinary bladder		(70)	(52)	(53)	(70)
bacterial colonies	- moderate	0	0	0	1
calculus/calculi	- no grade	0	2	0	0
dilatation	- moderate	2	1	4	2
erosion/ulcer	- moderate	1	0	0	0
hemorrhage		2	0	3	2
	- minimal	0	0	0	1
	- mild	0	0	1	0
	- moderate	0	0	1	0
	- severe	2	0	1	1
hyperplasia, papillary/nodular transitional cell	- moderate	1	2	0	1

( ) - Number observed

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Incidences of Microscopic Observations - MALE
Terminal

Tissue / Observation	Severity	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
Number of Animals Examined		70	70	70	70
urinary bladder		(70)	(52)	(53)	(70)
hyperplasia, simple transitional cell		3	3	6	2
	- minimal	2	1	2	0
	- mild	1	2	2	1
	- moderate	0	0	2	1
inflammation		6	6	6	4
	- minimal	2	2	1	1
	- mild	1	3	2	1
	- moderate	1	1	3	2
	- severe	2	0	0	0
inflammation, acute	- mild	0	0	1	0
inflammation, peritoneal	- mild	0	1	1	0
leukemia, granulocytic, malignant, multicentric		1	0	1	0
sarcoma, histiocytic, malignant, multicentric		0	0	1	2
within normal limits		63	45	43	64
zymbal`s gland		(0)	(0)	(0)	(1)
within normal limits		0	0	0	1

( ) - Number observed

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Incidences of Microscopic Observations - FEMALE
Terminal

Tissue / Observation	Severity	0 mg/kg/day	1 mg/kg/day	50 mg/kg/day	500 mg/kg/day
Number of Animals Examined		70	70	70	70
adrenal glands		(70)	(70)	(70)	(70)
adenoma, cortical, benign, primary		0	2	1	2
angiectasis/cystic degeneration, focal cortical		64	64	61	60
	- minimal	15	13	15	16
	- mild	25	25	22	20
	- moderate	23	24	21	18
	- severe	1	2	3	6
atrophy, cortical		1	0	2	2
	- mild	0	0	0	1
	- moderate	0	0	2	1
	- severe	1	0	0	0
ganglioneuroma, benign, primary		1	0	0	0
hematopoiesis, extramedullary		1	1	3	1
	- minimal	1	0	3	1
	- mild	0	1	0	0
hyperplasia, focal cortical		8	15	10	3
	- minimal	4	11	7	2
	- mild	4	4	3	1

( ) - Number observed

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Incidences of Microscopic Observations - FEMALE
Terminal

Tissue / Observation	Severity	0 mg/kg/day	1 mg/kg/day	50 mg/kg/day	500 mg/kg/day
Number of Animals Examined		70	70	70	70
adrenal glands		(70)	(70)	(70)	(70)
hyperplasia, focal medullary		6	8	8	10
	- minimal	3	6	5	6
	- mild	3	2	2	3
	- moderate	0	0	1	1
hypertrophy, focal cortical	- minimal	0	0	1	0
pheochromocytoma, benign, primary		0	2	1	4
pheochromocytoma, malignant, primary		0	0	0	1
vacuolation, focal		2	1	1	2
	- minimal	1	1	1	2
	- mild	1	0	0	0
within normal limits		4	3	8	7
aorta		(70)	(48)	(55)	(70)
mineralization	- mild	1	0	0	0
within normal limits		69	48	55	70
bile duct, extrahepatic		(0)	(0)	(0)	(1)
calculus/calculi	- moderate	0	0	0	1
dilatation	- moderate	0	0	0	1
bone		(0)	(0)	(1)	(0)
osteosarcoma, malignant, primary		0	0	1	0

( ) - Number observed

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Incidences of Microscopic Observations - FEMALE
Terminal

Tissue / Observation	Severity	0 mg/kg/day	1 mg/kg/day	50 mg/kg/day	500 mg/kg/day
Number of Animals Examined		70	70	70	70
bone marrow, femur		(70)	(48)	(55)	(70)
bacterial colonies	- mild	0	0	0	1
hyperplasia, granulocytic		13	14	5	15
	- minimal	1	1	0	2
	- mild	12	13	5	13
hyperplasia, mixed	- mild	2	0	0	0
lymphoma, malignant, multicentric		0	0	1	0
within normal limits		55	34	49	55
bone marrow, sternum		(70)	(48)	(55)	(70)
angiectasis	- mild	1	0	0	0
hyperplasia, granulocytic		11	10	5	6
	- minimal	6	6	3	3
	- mild	5	4	2	3
hyperplasia, mixed	- mild	1	0	0	0
lymphoma, malignant, multicentric		0	0	1	0
proliferation, fibro-osseous	- moderate	0	0	0	1
within normal limits		57	38	49	63
bone, femur		(70)	(48)	(55)	(70)
hyperostosis	- minimal	0	0	0	1
within normal limits		70	48	55	69

( ) - Number observed

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Incidences of Microscopic Observations - FEMALE
Terminal

Tissue / Observation	Severity	0 mg/kg/day	1 mg/kg/day	50 mg/kg/day	500 mg/kg/day
Number of Animals Examined		70	70	70	70
bone, sternum		(70)	(48)	(55)	(70)
hyperostosis	- mild	0	0	0	1
within normal limits		70	48	55	69
bone, tibia		(0)	(0)	(0)	(1)
proliferation, fibro-osseous	- mild	0	0	0	1
brain		(70)	(48)	(55)	(70)
astrocytoma, malignant, primary		1	0	0	0
bacterial colonies	- minimal	0	0	0	1
carcinoma, pars distalis, malignant, secondary		5	3	0	0
compression, ventral (pituitary tumor)		32	31	35	19
	- minimal	1	2	1	2
	- mild	9	4	11	8
	- moderate	18	24	22	9
	- severe	4	1	1	0
hemorrhage		2	5	0	0
	- minimal	0	3	0	0
	- mild	0	1	0	0
	- moderate	2	1	0	0
inflammation, embolic	- minimal	0	0	0	1
lymphoma, malignant, multicentric		1	0	0	0

( ) - Number observed

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Incidences of Microscopic Observations - FEMALE
Terminal

Tissue / Observation	Severity	0 mg/kg/day	1 mg/kg/day	50 mg/kg/day	500 mg/kg/day
Number of Animals Examined		70	70	70	70
brain		(70)	(48)	(55)	(70)
within normal limits		34	17	20	50
cavity, abdominal		(0)	(1)	(0)	(2)
adenocarcinoma, malignant, secondary		0	0	0	1
mesothelioma, malignant, secondary		0	1	0	0
sarcoma, stromal, malignant, secondary		0	0	0	1
cavity, thoracic		(0)	(1)	(0)	(1)
hemorrhage	- severe	0	0	0	1
inflammation, granulomatous	- moderate	0	1	0	0
clitoral glands		(0)	(1)	(0)	(0)
carcinoma, squamous cell, malignant, primary		0	1	0	0
esophagus		(70)	(48)	(55)	(70)
within normal limits		70	48	55	70
eyes		(69)	(48)	(55)	(70)
cataract		0	0	0	3
	- mild	0	0	0	2
	- moderate	0	0	0	1
inflammation, acute	- moderate	0	0	1	0

( ) - Number observed

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Incidences of Microscopic Observations - FEMALE
Terminal

Tissue / Observation	Severity	0 mg/kg/day	1 mg/kg/day	50 mg/kg/day	500 mg/kg/day
Number of Animals Examined		70	70	70	70
eyes		(69)	(48)	(55)	(70)
within normal limits		69	48	54	67
eyes, optic nerves		(69)	(48)	(55)	(70)
within normal limits		69	48	55	70
eyes, retina		(62)	(43)	(53)	(65)
degeneration/atrophy, retina, bilateral		1	2	1	0
	- minimal	0	0	1	0
	- mild	1	1	0	0
	- moderate	0	1	0	0
degeneration/atrophy, retina, unilateral		0	3	2	2
	- minimal	0	1	0	0
	- mild	0	0	2	2
	- moderate	0	2	0	0
detachment, retinal	- mild	0	0	0	1
fold/rosette, retinal	- minimal	0	1	0	0
within normal limits		61	38	50	62
galt		(69)	(48)	(55)	(68)
lymphoma, malignant, multicentric		1	0	0	0
within normal limits		68	48	55	68

( ) - Number observed

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Incidences of Microscopic Observations - FEMALE
Terminal

Tissue / Observation	Severity	0 mg/kg/day	1 mg/kg/day	50 mg/kg/day	500 mg/kg/day
Number of Animals Examined		70	70	70	70
harderian glands		(69)	(48)	(55)	(69)
hyperplasia, focal		6	1	2	2
	- minimal	6	1	2	1
	- mild	0	0	0	1
lymphoma, malignant, multicentric		1	0	0	0
within normal limits		62	47	53	67
heart		(70)	(48)	(55)	(70)
bacterial colonies	- mild	0	0	0	1
cardiomyopathy		39	27	23	35
	- minimal	37	25	23	33
	- mild	2	1	0	2
	- moderate	0	1	0	0
inflammation	- moderate	0	0	0	1
lymphoma, malignant, multicentric		1	0	1	0
schwannoma, malignant, primary		0	0	1	0
thrombus		0	1	0	1
	- moderate	0	0	0	1
	- severe	0	1	0	0
within normal limits		31	21	30	34

( ) - Number observed

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Incidences of Microscopic Observations - FEMALE
Terminal

Tissue / Observation	Severity	0 mg/kg/day	1 mg/kg/day	50 mg/kg/day	500 mg/kg/day
Number of Animals Examined		70	70	70	70
joint, tibiofemoral		(70)	(48)	(55)	(70)
lymphoma, malignant, multicentric		0	0	1	0
within normal limits		70	48	54	70
kidneys		(70)	(70)	(70)	(70)
adenocarcinoma, malignant, secondary		0	0	0	1
bacterial colonies	- minimal	0	0	0	1
cyst		1	2	1	4
	- minimal	1	1	1	2
	- mild	0	1	0	1
	- moderate	0	0	0	1
dilatation, tubular		4	2	5	28
	- minimal	3	0	0	11
	- mild	1	2	5	15
	- moderate	0	0	0	2
edema, papilla		4	1	2	43
	- minimal	1	1	2	23
	- mild	3	0	0	20
fibrosis	- severe	0	0	0	1
hyaline, droplets, increased	- mild	0	0	2	0
hydronephrosis, bilateral	- mild	1	2	0	2

( ) - Number observed

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Incidences of Microscopic Observations - FEMALE
Terminal

Tissue / Observation	Severity	0 mg/kg/day	1 mg/kg/day	50 mg/kg/day	500 mg/kg/day
Number of Animals Examined		70	70	70	70
kidneys		(70)	(70)	(70)	(70)
hydronephrosis, unilateral		5	2	2	4
	- minimal	0	1	1	0
	- mild	4	1	1	4
	- moderate	1	0	0	0
hyperplasia, transitional cell		6	3	12	33
	- minimal	5	2	11	29
	- mild	1	1	1	4
hyperplasia, tubular	- minimal	0	2	0	0
infarct	- minimal	0	1	0	0
inflammation, acute	- mild	0	0	0	1
inflammation, embolic	- minimal	0	0	0	1
lymphoma, malignant, multicentric		0	0	1	0
macrophages, pigmented	- minimal	1	0	0	0
mineralization, pelvic		52	63	58	63
	- minimal	47	52	54	51
	- mild	5	11	4	12
mineralization, tubular		25	32	28	42
	- minimal	25	31	28	37
	- mild	0	1	0	5

( ) - Number observed

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Incidences of Microscopic Observations - FEMALE
Terminal

Tissue / Observation	Severity	0 mg/kg/day	1 mg/kg/day	50 mg/kg/day	500 mg/kg/day
Number of Animals Examined		70	70	70	70
kidneys		(70)	(70)	(70)	(70)
necrosis, papillary		0	0	0	16
	- minimal	0	0	0	1
	- mild	0	0	0	3
	- moderate	0	0	0	6
	- severe	0	0	0	6
nephropathy, chronic progressive		39	40	41	64
	- minimal	29	32	32	15
	- mild	9	6	8	45
	- moderate	1	2	1	4
polyarteritis	- moderate	0	0	1	0
pyelitis		11	10	15	4
	- minimal	10	9	12	4
	- mild	1	1	3	0
within normal limits		3	0	3	0
lacrimal glands, exorbital		(69)	(48)	(55)	(70)
atrophy	- minimal	0	1	0	0
depletion, secretory	- severe	0	0	0	1
lymphoma, malignant, multicentric		1	0	0	0
within normal limits		68	47	55	69

( ) - Number observed

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Incidences of Microscopic Observations - FEMALE
Terminal

Tissue / Observation	Severity	0 mg/kg/day	1 mg/kg/day	50 mg/kg/day	500 mg/kg/day
Number of Animals Examined		70	70	70	70
large intestine, cecum		(70)	(48)	(55)	(70)
erosion/ulcer		1	1	0	0
	- mild	1	0	0	0
	- moderate	0	1	0	0
hypertrophy/hyperplasia, goblet cell	- moderate	0	0	0	1
polyarteritis	- minimal	2	0	0	0
within normal limits		67	47	55	69
large intestine, colon		(70)	(48)	(55)	(70)
hypertrophy/hyperplasia, goblet cell	- moderate	0	0	0	1
lymphoma, malignant, multicentric		1	0	0	0
within normal limits		69	48	55	69
large intestine, rectum		(70)	(48)	(55)	(70)
hypertrophy/hyperplasia, goblet cell	- moderate	0	0	0	1
within normal limits		70	48	55	69
larynx		(69)	(48)	(55)	(70)
exudate, luminal	- minimal	0	0	1	0
foreign material	- moderate	0	1	0	0
inflammation	- minimal	0	0	2	0
lymphoma, malignant, multicentric		1	0	0	0
mucus increased	- mild	0	1	0	0

( ) - Number observed

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Incidences of Microscopic Observations - FEMALE
Terminal

Tissue / Observation	Severity	0 mg/kg/day	1 mg/kg/day	50 mg/kg/day	500 mg/kg/day
Number of Animals Examined		70	70	70	70
larynx		(69)	(48)	(55)	(70)
within normal limits		68	47	53	70
liver		(70)	(70)	(70)	(70)
adenoma, hepatocellular, benign, primary		0	0	0	11
angiectasis		1	0	3	5
	- minimal	1	0	0	3
	- mild	0	0	3	2
carcinoma, hepatocellular, malignant, primary		0	0	0	4
cyst, biliary, simple		2	1	0	0
	- mild	2	0	0	0
	- moderate	0	1	0	0
degeneration, cystic, focal		2	2	2	14
	- minimal	2	2	2	12
	- mild	0	0	0	2
dilatation, cystic, bile ducts		2	0	0	0
	- minimal	1	0	0	0
	- mild	1	0	0	0
dilatation, sinusoidal	- minimal	0	0	1	0
fibrosis		1	0	2	1
	- minimal	1	0	2	0
	- severe	0	0	0	1

( ) - Number observed

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Incidences of Microscopic Observations - FEMALE
Terminal

Tissue / Observation	Severity	0 mg/kg/day	1 mg/kg/day	50 mg/kg/day	500 mg/kg/day
Number of Animals Examined		70	70	70	70
liver		(70)	(70)	(70)	(70)
focus of cellular alteration, basophilic		30	26	32	19
	- minimal	24	20	24	13
	- mild	6	6	8	4
	- moderate	0	0	0	2
focus of cellular alteration, clear		2	1	3	2
	- minimal	1	1	3	2
	- mild	1	0	0	0
focus of cellular alteration, eosinophilic		10	6	12	12
	- minimal	8	5	8	8
	- mild	1	1	4	1
	- moderate	1	0	0	3
hematopoiesis, extramedullary		13	26	24	11
	- minimal	13	25	24	11
	- mild	0	1	0	0
hyperplasia, bile duct		34	34	34	28
	- minimal	29	31	34	26
	- mild	5	3	0	2
hypertrophy, hepatocyte, centrilobular		0	0	3	65
	- minimal	0	0	3	52
	- mild	0	0	0	13
hypertrophy, hepatocyte, panlobular	- mild	0	0	0	3
infiltration, mononuclear cell	- minimal	18	11	9	17

( ) - Number observed

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Incidences of Microscopic Observations - FEMALE
Terminal

Tissue / Observation	Severity	0 mg/kg/day	1 mg/kg/day	50 mg/kg/day	500 mg/kg/day
Number of Animals Examined		70	70	70	70
liver		(70)	(70)	(70)	(70)
infiltration/inflammation, mixed cell	- minimal	1	0	0	0
inflammation, acute	- minimal	1	0	0	0
inflammation, chronic-active	- moderate	0	0	0	1
leukocytosis, sinusoidal		0	1	0	1
	- minimal	0	0	0	1
	- mild	0	1	0	0
lymphoma, malignant, multicentric		1	0	2	0
macrophages, pigmented	- minimal	1	0	0	2
multinucleated, hepatocytes		2	1	0	0
	- minimal	1	1	0	0
	- mild	1	0	0	0
necrosis	- moderate	0	1	0	0
necrosis, focal		5	4	6	8
	- minimal	4	3	5	5
	- mild	0	1	1	2
	- moderate	1	0	0	1
necrosis, hepatocytes, centrilobular		1	1	4	7
	- minimal	1	0	0	0
	- mild	0	0	1	3
	- moderate	0	0	2	4
	- severe	0	1	1	0

( ) - Number observed

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Incidences of Microscopic Observations - FEMALE
Terminal

Tissue / Observation	Severity	0 mg/kg/day	1 mg/kg/day	50 mg/kg/day	500 mg/kg/day
Number of Animals Examined		70	70	70	70
liver		(70)	(70)	(70)	(70)
necrosis, individual hepatocyte		0	0	0	3
	- minimal	0	0	0	1
	- mild	0	0	0	2
vacuolation, centrilobular		3	1	0	0
	- minimal	2	1	0	0
	- moderate	1	0	0	0
vacuolation, diffuse	- mild	1	0	0	0
vacuolation, focal	- minimal	1	1	0	1
vacuolation, median cleft	- mild	1	1	0	1
vacuolation, periportal		17	23	22	2
	- minimal	10	17	18	2
	- mild	6	6	4	0
	- moderate	1	0	0	0
within normal limits		7	9	9	0
lung		(70)	(70)	(70)	(70)
adenocarcinoma, malignant, secondary		1	0	0	2
bacterial colonies	- minimal	2	0	1	0
congestion, chronic passive	- severe	0	0	1	0
fibrosis	- minimal	0	0	0	1
foreign material	- mild	0	2	0	0
granuloma	- minimal	1	0	0	1

( ) - Number observed

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Incidences of Microscopic Observations - FEMALE
Terminal

Tissue / Observation	Severity	0 mg/kg/day	1 mg/kg/day	50 mg/kg/day	500 mg/kg/day
Number of Animals Examined		70	70	70	70
lung		(70)	(70)	(70)	(70)
hemorrhage		1	0	0	1
	- minimal	1	0	0	0
	- mild	0	0	0	1
histiocytosis, alveolar		22	20	21	42
	- minimal	20	20	21	34
	- mild	2	0	0	8
infiltration, lymphoid, perivascular	- mild	1	0	0	0
inflammation, acute		0	3	0	1
	- minimal	0	0	0	1
	- moderate	0	2	0	0
	- severe	0	1	0	0
inflammation, subacute/chronic	- minimal	1	3	1	0
leukocytosis, vascular	- mild	0	1	0	0
lymphoma, malignant, multicentric		1	0	1	0
macrophages, pigmented alveolar		1	0	0	1
	- minimal	1	0	0	0
	- mild	0	0	0	1
mucus increased	- mild	0	1	0	0
within normal limits		42	44	47	26

( ) - Number observed

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Incidences of Microscopic Observations - FEMALE
Terminal

Tissue / Observation	Severity	0 mg/kg/day	1 mg/kg/day	50 mg/kg/day	500 mg/kg/day
Number of Animals Examined		70	70	70	70
lymph node, axillary		(23)	(22)	(18)	(12)
erythrocytosis/erythrophagocytosis, sinus		1	0	0	1
	- minimal	1	0	0	0
	- mild	0	0	0	1
histiocytosis, sinus	- mild	1	1	1	0
hyperplasia, lymphocyte/plasmacyte, medulla	- mild	1	2	1	1
within normal limits		21	19	16	10
lymph node, hepatic		(0)	(0)	(0)	(4)
within normal limits		0	0	0	4
lymph node, iliac		(1)	(4)	(3)	(7)
dilatation, sinus	- minimal	0	0	1	0
hyperplasia, lymphocyte/plasmacyte, medulla	- mild	0	1	0	0
within normal limits		1	3	2	7
lymph node, inguinal		(10)	(15)	(13)	(8)
lymphoma, malignant, multicentric		1	0	0	0
within normal limits		9	15	13	8
lymph node, mandibular		(69)	(51)	(56)	(69)
dilatation, sinus	- minimal	0	1	0	1

( ) - Number observed

MPI Research Study Number 125-141
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H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Incidences of Microscopic Observations - FEMALE
Terminal

Tissue / Observation	Severity	0 mg/kg/day	1 mg/kg/day	50 mg/kg/day	500 mg/kg/day
Number of Animals Examined		70	70	70	70
lymph node, mandibular		(69)	(51)	(56)	(69)
erythrocytosis/erythrophagocytosis, sinus		16	11	14	8
	- minimal	9	5	13	8
	- mild	7	6	0	0
	- moderate	0	0	1	0
hyperplasia, lymphocyte/plasmacyte, medulla	- mild	1	1	0	1
lymphoma, malignant, multicentric		1	0	1	0
within normal limits		52	39	41	59
lymph node, mediastinal		(1)	(0)	(2)	(1)
hyperplasia, lymphocyte/plasmacyte, medulla	- mild	0	0	0	1
lymphoma, malignant, multicentric		0	0	1	0
within normal limits		1	0	1	0
lymph node, mesenteric		(70)	(48)	(56)	(70)
dilatation, sinus		2	0	1	0
	- minimal	1	0	0	0
	- mild	0	0	1	0
	- moderate	1	0	0	0
erythrocytosis/erythrophagocytosis, sinus		1	0	1	0
	- minimal	1	0	0	0
	- mild	0	0	1	0
hyperplasia, lymphocyte/plasmacyte, medulla	- moderate	0	0	0	1

( ) - Number observed

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H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Incidences of Microscopic Observations - FEMALE
Terminal

Tissue / Observation	Severity	0 mg/kg/day	1 mg/kg/day	50 mg/kg/day	500 mg/kg/day
Number of Animals Examined		70	70	70	70
lymph node, mesenteric		(70)	(48)	(56)	(70)
lymphoma, malignant, multicentric		1	0	1	0
within normal limits		66	48	54	69
mammary gland		(70)	(67)	(66)	(70)
abscess	- severe	1	0	0	0
adenocarcinoma, malignant, primary		23	26	23	21
adenoma, benign, primary		4	3	2	2
dilatation, gland/lumen	- mild	1	0	0	0
fibroadenoma, benign, primary		34	30	24	23
galactocele		0	3	1	0
	- mild	0	3	0	0
	- moderate	0	0	1	0
hyperplasia, lobular		64	47	56	62
	- minimal	15	9	17	20
	- mild	41	34	37	40
	- moderate	8	4	2	2
within normal limits		4	2	1	5
mesentery/peritoneum		(1)	(2)	(0)	(1)
congestion	- mild	0	1	0	0

( ) - Number observed

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H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Incidences of Microscopic Observations - FEMALE
Terminal

Tissue / Observation	Severity	0 mg/kg/day	1 mg/kg/day	50 mg/kg/day	500 mg/kg/day
Number of Animals Examined		70	70	70	70
mesentery/peritoneum		(1)	(2)	(0)	(1)
necrosis, fat		0	1	0	1
	- mild	0	0	0	1
	- moderate	0	1	0	0
polyarteritis	- moderate	1	0	0	0
multicentric neoplasm		(1)	(0)	(4)	(0)
lymphoma, malignant, multicentric		1	0	4	0
nerve, sciatic		(70)	(48)	(55)	(70)
degeneration, axonal/myelin		37	21	23	39
	- minimal	37	20	23	39
	- mild	0	1	0	0
inflammation, subacute/chronic	- minimal	0	1	0	0
within normal limits		33	27	32	31
nose, level a		(70)	(48)	(55)	(70)
exudate, nasal passage		0	5	2	1
	- minimal	0	2	0	1
	- mild	0	3	1	0
	- moderate	0	0	1	0

( ) - Number observed

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Incidences of Microscopic Observations - FEMALE
Terminal

Tissue / Observation	Severity	0 mg/kg/day	1 mg/kg/day	50 mg/kg/day	500 mg/kg/day
Number of Animals Examined		70	70	70	70
nose, level a		(70)	(48)	(55)	(70)
foreign material		1	2	1	0
	- minimal	0	2	1	0
	- mild	1	0	0	0
hyperostosis	- minimal	0	0	0	1
inflammation		1	0	1	3
	- minimal	1	0	0	2
	- mild	0	0	1	1
inflammation, hair follicle/epidermis	- minimal	0	0	0	1
lymphoma, malignant, multicentric		1	0	0	0
within normal limits		67	43	53	65
nose, level b		(70)	(48)	(55)	(70)
degeneration	- mild	1	0	0	0
exudate, nasal passage		2	6	1	1
	- minimal	2	4	0	1
	- mild	0	2	0	0
	- moderate	0	0	1	0
foreign material		1	5	0	0
	- minimal	0	4	0	0
	- mild	0	1	0	0
	- moderate	1	0	0	0
hyperostosis	- mild	0	0	0	1

( ) - Number observed

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H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Incidences of Microscopic Observations - FEMALE
Terminal

Tissue / Observation	Severity	0 mg/kg/day	1 mg/kg/day	50 mg/kg/day	500 mg/kg/day
Number of Animals Examined		70	70	70	70
nose, level b		(70)	(48)	(55)	(70)
inflammation	- minimal	0	0	1	1
lymphoma, malignant, multicentric		1	0	1	0
metaplasia, squamous	- minimal	0	0	0	1
mucus increased	- minimal	0	1	0	0
within normal limits		65	40	53	68
nose, level c		(70)	(48)	(55)	(70)
erosion/ulcer	- moderate	0	0	0	1
exudate, nasal passage		0	3	1	1
	- minimal	0	2	1	0
	- mild	0	1	0	0
	- moderate	0	0	0	1
foreign material		2	2	0	1
	- minimal	0	2	0	0
	- mild	1	0	0	1
	- moderate	1	0	0	0
hyperostosis	- mild	0	0	0	1
inflammation	- mild	0	0	0	1
lymphoma, malignant, multicentric		1	0	1	0
mucus increased	- mild	0	0	1	0
within normal limits		67	44	52	67

( ) - Number observed

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Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Incidences of Microscopic Observations - FEMALE
Terminal

Tissue / Observation	Severity	0 mg/kg/day	1 mg/kg/day	50 mg/kg/day	500 mg/kg/day
Number of Animals Examined		70	70	70	70
nose, level d		(70)	(48)	(55)	(70)
degeneration/necrosis, olfactory epithelium	- minimal	0	0	1	0
erosion/ulcer	- moderate	0	0	0	1
exudate, nasal passage		0	2	1	1
	- minimal	0	1	1	0
	- mild	0	1	0	0
	- moderate	0	0	0	1
foreign material		1	2	0	1
	- minimal	1	1	0	0
	- mild	0	1	0	1
hyperostosis	- mild	0	0	0	1
inflammation	- mild	0	0	0	1
lymphoma, malignant, multicentric		1	0	1	0
mucus increased	- mild	0	0	1	0
within normal limits		68	45	51	67
ovaries		(70)	(50)	(56)	(70)
cyst		16	16	11	13
	- minimal	11	5	4	6
	- mild	5	10	7	7
	- moderate	0	1	0	0
fibrosis	- moderate	0	0	0	1

( ) - Number observed

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H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Incidences of Microscopic Observations - FEMALE
Terminal

Tissue / Observation	Severity	0 mg/kg/day	1 mg/kg/day	50 mg/kg/day	500 mg/kg/day
Number of Animals Examined		70	70	70	70
ovaries		(70)	(50)	(56)	(70)
hemangiosarcoma, malignant, primary		0	0	0	1
hyperplasia, sex-cord/stromal		9	1	4	3
	- minimal	5	0	2	1
	- mild	4	1	2	2
luteoma, benign, primary		0	1	0	0
mesothelioma, malignant, primary		0	1	0	0
sex-cord/stromal tumor, malignant, primary		0	0	1	0
within normal limits		48	32	43	53
oviducts		(70)	(48)	(55)	(69)
within normal limits		70	48	55	69
pancreas		(70)	(70)	(70)	(70)
adenoma, islet cell, benign, primary		3	2	2	3
atrophy, acinar		9	16	10	7
	- minimal	8	13	7	6
	- mild	1	3	3	1
bacterial colonies	- severe	0	0	0	1
carcinoma, islet cell, malignant, primary		1	0	0	0
dilatation, duct	- mild	0	0	1	0
fibrosis	- minimal	4	0	2	1

( ) - Number observed

MPI Research Study Number 125-141
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H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Incidences of Microscopic Observations - FEMALE
Terminal

Tissue / Observation	Severity	0 mg/kg/day	1 mg/kg/day	50 mg/kg/day	500 mg/kg/day
Number of Animals Examined		70	70	70	70
pancreas		(70)	(70)	(70)	(70)
hyperplasia, acinar cell, focal		0	2	5	5
	- minimal	0	1	3	2
	- mild	0	1	1	2
	- moderate	0	0	1	1
hyperplasia, islet cell		1	2	1	0
	- minimal	0	0	1	0
	- mild	1	2	0	0
lymphoma, malignant, multicentric		1	0	0	0
polyarteritis		2	0	2	1
	- mild	0	0	0	1
	- moderate	2	0	2	0
within normal limits		52	50	53	55
parathyroid glands		(53)	(37)	(41)	(53)
adenoma, benign, primary		0	1	0	0
hyperplasia, focal		3	1	1	1
	- minimal	2	0	0	1
	- mild	1	1	1	0
within normal limits		50	35	40	52
pharynx		(70)	(48)	(55)	(70)
within normal limits		70	48	55	70

( ) - Number observed

MPI Research Study Number 125-141
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H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Incidences of Microscopic Observations - FEMALE
Terminal

Tissue / Observation	Severity	0 mg/kg/day	1 mg/kg/day	50 mg/kg/day	500 mg/kg/day
Number of Animals Examined		70	70	70	70
pituitary gland		(70)	(65)	(65)	(70)
adenoma, pars distalis, benign, primary		53	58	58	52
carcinoma, pars distalis, malignant, primary		5	3	0	0
cyst		1	0	0	2
	- minimal	0	0	0	1
	- mild	0	0	0	1
	- moderate	1	0	0	0
hyperplasia, diffuse, pars distalis	- mild	3	1	1	3
hyperplasia, focal, pars distalis		2	0	0	4
	- minimal	0	0	0	2
	- mild	2	0	0	2
within normal limits		7	3	7	10
salivary gland, mandibular		(69)	(47)	(54)	(69)
atrophy	- moderate	1	0	0	0
lymphoma, malignant, multicentric		1	0	0	0
within normal limits		67	47	54	69
salivary gland, parotid		(69)	(48)	(54)	(70)
atrophy	- minimal	0	1	0	0
edema	- mild	0	0	0	1
lymphoma, malignant, multicentric		1	0	0	0

( ) - Number observed

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Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Incidences of Microscopic Observations - FEMALE
Terminal

Tissue / Observation	Severity	0 mg/kg/day	1 mg/kg/day	50 mg/kg/day	500 mg/kg/day
Number of Animals Examined		70	70	70	70
salivary gland, parotid		(69)	(48)	(54)	(70)
within normal limits		68	47	54	69
salivary gland, sublingual		(69)	(47)	(54)	(68)
lymphoma, malignant, multicentric		1	0	0	0
within normal limits		68	47	54	68
skeletal muscle		(0)	(0)	(1)	(0)
lymphoma, malignant, multicentric		0	0	1	0
skeletal muscle, biceps femoris		(70)	(48)	(55)	(70)
degeneration/necrosis, myofiber	- minimal	15	0	4	14
degeneration/regeneration, myofiber	- minimal	0	1	0	1
lymphoma, malignant, multicentric		1	0	0	0
within normal limits		54	47	51	55
skin		(70)	(48)	(55)	(70)
adenoma, basal cell, benign, primary		1	0	0	0
alopecia/hypotrichosis		1	2	5	9
	- mild	1	0	5	6
	- moderate	0	2	0	3
carcinoma, squamous cell, malignant, primary		0	0	1	0
cyst, keratin	- minimal	0	1	1	0

( ) - Number observed

MPI Research Study Number 125-141
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H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Incidences of Microscopic Observations - FEMALE
Terminal

Tissue / Observation	Severity	0 mg/kg/day	1 mg/kg/day	50 mg/kg/day	500 mg/kg/day
Number of Animals Examined		70	70	70	70
skin		(70)	(48)	(55)	(70)
erosion/ulcer	- moderate	1	0	0	0
hyperplasia, epidermal		0	1	1	0
	- mild	0	1	0	0
	- moderate	0	0	1	0
keratoacanthoma, benign, primary		0	0	0	1
within normal limits		67	44	48	60
skin, subcutis		(6)	(4)	(2)	(4)
abscess	- mild	0	0	0	1
fibroma, benign, primary		3	2	0	1
fibrosarcoma, malignant, primary		1	1	2	2
lymphoma, malignant, multicentric		1	0	0	0
schwannoma, benign, primary		1	0	0	0
schwannoma, malignant, primary		0	1	0	0
small intestine, duodenum		(70)	(48)	(55)	(70)
hypertrophy/hyperplasia, goblet cell	- mild	0	0	0	1
within normal limits		70	48	55	69
small intestine, ileum		(70)	(48)	(55)	(70)
hypertrophy/hyperplasia, goblet cell	- moderate	0	0	0	1
within normal limits		70	48	55	69

( ) - Number observed

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H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Incidences of Microscopic Observations - FEMALE
Terminal

Tissue / Observation	Severity	0 mg/kg/day	1 mg/kg/day	50 mg/kg/day	500 mg/kg/day
Number of Animals Examined		70	70	70	70
small intestine, jejunum		(70)	(48)	(55)	(70)
hypertrophy/hyperplasia, goblet cell	- moderate	0	0	0	1
within normal limits		70	48	55	69
spinal cord, cervical		(70)	(48)	(55)	(70)
within normal limits		70	48	55	70
spinal cord, lumbar		(70)	(48)	(55)	(70)
within normal limits		70	48	55	70
spinal cord, thoracic		(70)	(48)	(55)	(70)
degeneration, axonal/myelin	- mild	0	0	0	1
within normal limits		70	48	55	69
spleen		(70)	(48)	(57)	(70)
depletion, lymphoid, generalized	- moderate	0	0	0	2
fibrosis, capsular	- mild	0	0	1	0
hematopoiesis, extramedullary, increased		31	20	25	40
	- minimal	22	9	11	23
	- mild	8	7	12	14
	- moderate	1	4	2	3
lymphoma, malignant, multicentric		1	0	1	0

( ) - Number observed

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Incidences of Microscopic Observations - FEMALE
Terminal

Tissue / Observation	Severity	0 mg/kg/day	1 mg/kg/day	50 mg/kg/day	500 mg/kg/day
Number of Animals Examined		70	70	70	70
spleen		(70)	(48)	(57)	(70)
within normal limits		38	28	32	28
stomach, glandular		(70)	(48)	(55)	(70)
erosion/ulcer	- mild	2	0	0	3
fibrosis	- mild	0	0	0	2
inflammation	- mild	1	0	0	0
leiomyoma, benign, primary		0	0	0	1
mineralization	- mild	0	0	0	1
within normal limits		68	48	55	64
stomach, nonglandular		(70)	(70)	(70)	(70)
cyst, keratin		1	1	0	2
	- minimal	1	1	0	0
	- moderate	0	0	0	2
edema	- mild	0	1	0	0
erosion/ulcer		1	0	2	0
	- minimal	1	0	0	0
	- moderate	0	0	1	0
	- severe	0	0	1	0
erosion/ulcer, limiting ridge		0	0	1	2
	- minimal	0	0	1	1
	- mild	0	0	0	1

( ) - Number observed

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H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Incidences of Microscopic Observations - FEMALE
Terminal

Tissue / Observation	Severity	0 mg/kg/day	1 mg/kg/day	50 mg/kg/day	500 mg/kg/day
Number of Animals Examined		70	70	70	70
stomach, nonglandular		(70)	(70)	(70)	(70)
hyperplasia, epithelial, limiting ridge		0	0	0	9
	- minimal	0	0	0	8
	- moderate	0	0	0	1
hyperplasia, epithelial, nonglandular		3	3	5	0
	- mild	0	2	1	0
	- moderate	3	1	4	0
inflammation		4	2	6	0
	- minimal	1	1	0	0
	- mild	3	1	5	0
	- moderate	0	0	1	0
lymphoma, malignant, multicentric		1	0	0	0
within normal limits		64	66	63	57
thymus		(68)	(48)	(55)	(67)
depletion, lymphoid, generalized		67	46	51	66
	- mild	0	2	1	1
	- moderate	52	29	34	38
	- severe	15	15	16	27
hyperplasia, epithelial cell		26	21	19	21
	- minimal	18	19	18	15
	- mild	8	2	1	6
hyperplasia, lymphoid, medulla	- mild	1	3	0	2

( ) - Number observed

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Incidences of Microscopic Observations - FEMALE
Terminal

Tissue / Observation	Severity	0 mg/kg/day	1 mg/kg/day	50 mg/kg/day	500 mg/kg/day
Number of Animals Examined		70	70	70	70
thymus		(68)	(48)	(55)	(67)
lymphoma, malignant, multicentric		0	0	2	0
thymoma, malignant, primary		1	1	0	0
within normal limits		0	0	2	1
thyroid gland		(69)	(48)	(55)	(70)
adenoma, c-cell, benign, primary		9	3	7	7
adenoma, follicular cell, benign, primary		0	0	0	1
carcinoma, c-cell, malignant, primary		0	0	1	0
carcinoma, follicular cell, malignant, primary		1	1	0	1
cyst, follicular	- mild	0	0	0	1
hyperplasia, c-cell, focal		10	3	6	7
	- minimal	4	1	3	4
	- mild	5	2	3	3
	- moderate	1	0	0	0
hyperplasia, follicular cell		1	0	0	2
	- minimal	1	0	0	1
	- mild	0	0	0	1
lymphoma, malignant, multicentric		1	0	0	0
within normal limits		49	41	42	54
tongue		(70)	(70)	(70)	(70)
carcinoma, squamous cell, malignant, primary		0	0	0	1

( ) - Number observed

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Incidences of Microscopic Observations - FEMALE
Terminal

Tissue / Observation	Severity	0 mg/kg/day	1 mg/kg/day	50 mg/kg/day	500 mg/kg/day
Number of Animals Examined		70	70	70	70
tongue		(70)	(70)	(70)	(70)
erosion/ulcer		0	1	1	1
	- minimal	0	1	0	0
	- mild	0	0	1	0
	- moderate	0	0	0	1
hyperplasia, squamous cell		2	8	4	13
	- minimal	0	0	0	1
	- mild	1	4	1	5
	- moderate	1	4	3	7
inflammation, acute	- minimal	1	0	0	0
inflammation, subacute/chronic		3	8	4	13
	- minimal	1	1	0	1
	- mild	1	7	4	11
	- moderate	1	0	0	1
within normal limits		66	62	66	56
trachea		(70)	(48)	(55)	(70)
inflammation, acute	- minimal	0	1	1	0
within normal limits		70	47	54	70

( ) - Number observed

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Incidences of Microscopic Observations - FEMALE
Terminal

Tissue / Observation	Severity	0 mg/kg/day	1 mg/kg/day	50 mg/kg/day	500 mg/kg/day
Number of Animals Examined		70	70	70	70
ureters		(70)	(47)	(54)	(69)
dilatation		4	2	0	2
	- mild	4	1	0	2
	- moderate	0	1	0	0
lymphoma, malignant, multicentric		1	0	0	0
within normal limits		65	45	54	67
urinary bladder		(69)	(48)	(55)	(70)
dilatation	- moderate	0	1	0	0
hemorrhage	- severe	0	1	0	0
hyperplasia, simple transitional cell		1	1	0	3
	- minimal	0	0	0	2
	- mild	0	1	0	1
	- moderate	1	0	0	0
inflammation		1	1	0	1
	- minimal	1	0	0	1
	- moderate	0	1	0	0
leiomyosarcoma, malignant, secondary		0	1	0	0
lymphoma, malignant, multicentric		1	0	0	0
within normal limits		67	46	55	67
uterus with cervix		(70)	(70)	(70)	(70)
adenocarcinoma, malignant, primary		0	0	1	0

( ) - Number observed

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Incidences of Microscopic Observations - FEMALE
Terminal

Tissue / Observation	Severity	0 mg/kg/day	1 mg/kg/day	50 mg/kg/day	500 mg/kg/day
Number of Animals Examined		70	70	70	70
uterus with cervix		(70)	(70)	(70)	(70)
carcinoma, squamous cell, malignant, primary		0	0	0	1
dilatation, gland/lumen		17	19	22	13
	- minimal	4	9	8	9
	- mild	11	8	12	4
	- moderate	2	2	2	0
granular cell tumor, benign, primary		2	0	1	1
hyperkeratosis		2	1	0	1
	- minimal	1	1	0	1
	- mild	1	0	0	0
hyperplasia, cervical fibromuscular		1	4	1	2
	- mild	0	2	1	1
	- moderate	1	2	0	1
hyperplasia, cystic endometrial	- mild	1	0	0	0
hyperplasia, endometrial	- mild	3	0	0	1
hyperplasia, squamous cell		4	3	1	4
	- minimal	0	2	1	1
	- mild	4	1	0	3
leiomyosarcoma, malignant, primary		0	1	0	0
lymphoma, malignant, multicentric		1	0	0	0
metaplasia, squamous		2	0	4	2
	- minimal	2	0	3	1
	- mild	0	0	1	1

( ) - Number observed

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Incidences of Microscopic Observations - FEMALE
Terminal

Tissue / Observation	Severity	0 mg/kg/day	1 mg/kg/day	50 mg/kg/day	500 mg/kg/day
Number of Animals Examined		70	70	70	70
uterus with cervix		(70)	(70)	(70)	(70)
polyp, glandular, benign, primary		0	1	0	0
polyp, stromal, benign, primary		1	2	1	7
sarcoma, stromal, malignant, primary		0	0	0	1
schwannoma, malignant, primary		0	0	0	1
thrombus	- mild	0	0	1	0
within normal limits		45	44	44	42
vagina		(70)	(48)	(55)	(70)
granular cell tumor, benign, primary		1	1	1	1
hyperplasia, fibromuscular	- moderate	1	0	0	1
prolapse	- no grade	1	0	0	0
within normal limits		68	47	54	68
zymbal`s gland		(1)	(0)	(0)	(0)
carcinoma, sebaceous cell, malignant, primary		1	0	0	0

( ) - Number observed

Table 5
Incidences of Primary Tumors

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Incidences of Primary Tumors - MALE

Terminal

Tissue / Diagnosis	0 mg/kg/day			0.1 mg/kg/day			1 mg/kg/day			50 mg/kg/day		
	No. with Tumor	Animal No.	Fate/ Day	No. with Tumor	Animal No.	Fate/ Day	No. with Tumor	Animal No.	Fate/ Day	No. with Tumor	Animal No.	Fate/ Day
adipose tissue	(0)			(0)			(1)			(0)		
adrenal glands	(70)			(52)			(52)			(70)		
adenoma, cortical, benign, primary	2	1031	S 722	0			1	1187	D 549	1	1305	E 558
		1077	E 722									
carcinoma, cortical, malignant, primary	0			0			0			1	1304	D 543
pheochromocytoma, benign, primary	12	1025	S 722	9	1102	D 650	7	1173	E 553	9	1269	E 646
		1028	D 643		1110	E 687		1183	D 537		1271	D 722
		1030	D 598		1113	E 630		1195	E 602		1286	S 722
		1031	S 722		1118	E 590		1198	E 628		1289	S 723
		1041	S 722		1120	S 722		1202	E 722		1293	D 623
		1054	E 687		1126	E 687		1210	E 686		1294	S 723
		1055	E 602		1138	E 694		1229	E 664		1297	S 723
		1057	D 675		1142	D 391					1308	E 708
		1066	D 474		1159	E 708					1314	E 700
		1067	S 723									
		1068	S 723									
		1069	D 545									

S - Scheduled necropsy
E - Euthanized *in extremis*
D - Died on Study
( ) - Total number examined

No. - Number

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Incidences of Primary Tumors - MALE

Terminal

Tissue / Diagnosis	0 mg/kg/day No. with Tumor	Animal No.	Fate/ Day	0.1 mg/kg/day No. with Tumor	Animal No.	Fate/ Day	1 mg/kg/day No. with Tumor	Animal No.	Fate/ Day	50 mg/kg/day No. with Tumor	Animal No.	Fate/ Day
adrenal glands	(70)			(52)			(52)			(70)		
pheochromocytoma, malignant, primary	1	1072	D 692	2	1102 1122	D 650 S 723	0			2	1252 1289	S 722 S 723
aorta	(70)			(50)			(52)			(70)		
bile duct, extrahepatic	(1)			(0)			(1)			(0)		
bone	(1)			(1)			(0)			(0)		
osteosarcoma, malignant, primary	1	1055	E 602	1	1128	E 553	0			0		
bone marrow, femur	(70)			(50)			(52)			(70)		
bone marrow, sternum	(70)			(50)			(52)			(70)		
bone marrow, tibia	(1)			(0)			(0)			(0)		
bone, femur	(70)			(51)			(52)			(70)		
osteosarcoma, malignant, primary	1	1030	D 598	0			0			0		

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E - Euthanized *in extremis*
D - Died on Study
( ) - Total number examined

No. - Number

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Incidences of Primary Tumors - MALE

Terminal

Tissue / Diagnosis	0 mg/kg/day No. with Tumor	Animal No.	Fate/ Day	0.1 mg/kg/day No. with Tumor	Animal No.	Fate/ Day	1 mg/kg/day No. with Tumor	Animal No.	Fate/ Day	50 mg/kg/day No. with Tumor	Animal No.	Fate/ Day
bone, sternum	(70)			(50)			(52)			(70)		
lipoma, benign, primary	0			0			0			1	1253	E 610
brain	(70)			(50)			(52)			(70)		
astrocytoma, malignant, primary	1	1078	E 611	4	1104	D 435	1	1216	D 394	0		
					1148	E 574						
					1149	E 617						
					1159	E 708						
schwannoma, malignant, secondary	0			0			0			1	1317	E 392
cavity, abdominal	(1)			(1)			(2)			(3)		
fibrosarcoma, malignant, secondary	0			0			0			1	1288	E 617
cavity, thoracic	(5)			(0)			(2)			(1)		
osteosarcoma, malignant, secondary	1	1030	D 598	0			0			0		

E - Euthanized *in extremis*
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( ) - Total number examined
No. - Number

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Incidences of Primary Tumors - MALE

Terminal

Tissue / Diagnosis	0 mg/kg/day No. with Tumor	Animal No.	Fate/ Day	0.1 mg/kg/day No. with Tumor	Animal No.	Fate/ Day	1 mg/kg/day No. with Tumor	Animal No.	Fate/ Day	50 mg/kg/day No. with Tumor	Animal No.	Fate/ Day
coagulating glands	(70)			(50)			(53)			(70)		
epididymides	(70)			(50)			(52)			(70)		
mesothelioma, malignant, primary	0			1	1128	E 553	0			0		
esophagus	(70)			(50)			(52)			(70)		
eyes	(68)			(49)			(51)			(70)		
melanoma, amelanotic, malignant, primary	1	1025	S 722	0			0			0		
eyes, optic nerves	(70)			(49)			(51)			(70)		
schwannoma, malignant, primary	0			0			0			1	1317	E 392
eyes, retina	(63)			(42)			(43)			(63)		
foot/feet	(1)			(3)			(1)			(2)		

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E - Euthanized *in extremis*
( ) - Total number examined
No. - Number

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Incidences of Primary Tumors - MALE

Terminal

Tissue / Diagnosis	0 mg/kg/day No. with Tumor	Animal No.	Fate/ Day	0.1 mg/kg/day No. with Tumor	Animal No.	Fate/ Day	1 mg/kg/day No. with Tumor	Animal No.	Fate/ Day	50 mg/kg/day No. with Tumor	Animal No.	Fate/ Day
galt	(70)			(50)			(52)			(70)		
harderian glands	(68)			(50)			(52)			(70)		
head	(0)			(0)			(0)			(1)		
heart	(70)			(50)			(52)			(70)		
schwannoma, malignant, primary	0			1	1115	E 645	0			0		
hind limb/leg	(0)			(2)			(0)			(0)		
joint, tibiofemoral	(70)			(51)			(52)			(70)		
kidneys	(70)			(55)			(53)			(70)		
adenoma, tubular cell, benign, primary	2	1071 1073	E 708 E 666	0			0			0		
carcinoma, sebaceous cell, malignant, secondary	0			0			0			1	1278	D 614

E - Euthanized *in extremis*
D - Died on Study
( ) - Total number examined
No. - Number

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Incidences of Primary Tumors - MALE

Terminal

Tissue / Diagnosis	0 mg/kg/day			0.1 mg/kg/day			1 mg/kg/day			50 mg/kg/day		
	No. with Tumor	Animal No.	Fate/ Day	No. with Tumor	Animal No.	Fate/ Day	No. with Tumor	Animal No.	Fate/ Day	No. with Tumor	Animal No.	Fate/ Day
kidneys	(70)			(55)			(53)			(70)		
carcinoma, tubular cell, malignant, primary	0			2	1102 1127	D 650 S 723	0			0		
lacrimal glands, exorbital	(69)			(49)			(52)			(70)		
large intestine, cecum	(70)			(50)			(52)			(70)		
large intestine, colon	(70)			(50)			(52)			(70)		
large intestine, rectum	(70)			(50)			(52)			(70)		
larynx	(70)			(49)			(52)			(70)		
liver	(70)			(70)			(70)			(70)		
adenoma, hepatocellular, benign, primary	1	1062	S 723	2	1093 1143	S 722 S 723	1	1204	S 723	1	1270	S 722
carcinoma, hepatocellular, malignant, primary	1	1042	E 623	0			0			2	1262 1287	D 575 S 722

S - Scheduled necropsy
E - Euthanized *in extremis*
D - Died on Study
( ) - Total number examined

No. - Number

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Incidences of Primary Tumors - MALE

Terminal

Tissue / Diagnosis	0 mg/kg/day No. with Tumor	Animal No.	Fate/ Day	0.1 mg/kg/day No. with Tumor	Animal No.	Fate/ Day	1 mg/kg/day No. with Tumor	Animal No.	Fate/ Day	50 mg/kg/day No. with Tumor	Animal No.	Fate/ Day
liver	(70)			(70)			(70)			(70)		
osteosarcoma, malignant, secondary	1	1030	D 598	0			0			0		
lung	(70)			(50)			(53)			(70)		
adenocarcinoma (primary site unknown), malignant, primary	0			1	1158	E 628	0			0		
carcinoma, c-cell, malignant, secondary	1	1025	S 722	0			0			0		
carcinoma, cortical, malignant, secondary	0			0			0			1	1304	D 543
carcinoma, sebaceous cell (primary site unknown), malignant,	0			0			0			1	1278	D 614
hemangiosarcoma, malignant, secondary	0			1	1156	E 569	0			0		
osteosarcoma, malignant, secondary	1	1030	D 598	0			0			0		

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E - Euthanized *in extremis*
D - Died on Study
( ) - Total number examined

No. - Number

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Incidences of Primary Tumors - MALE

Terminal

Tissue / Diagnosis	0 mg/kg/day No. with Tumor	Animal No.	Fate/ Day	0.1 mg/kg/day No. with Tumor	Animal No.	Fate/ Day	1 mg/kg/day No. with Tumor	Animal No.	Fate/ Day	50 mg/kg/day No. with Tumor	Animal No.	Fate/ Day
lymph node, axillary	(12)			(5)			(6)			(8)		
lymph node, hepatic	(3)			(1)			(1)			(2)		
lymph node, iliac	(0)			(2)			(2)			(1)		
lymph node, inguinal	(1)			(5)			(5)			(0)		
lymph node, mandibular	(70)			(49)			(53)			(69)		
osteosarcoma, malignant, secondary	1	1055	E 602	0			0			0		
lymph node, mediastinal	(3)			(1)			(3)			(3)		
lymph node, mesenteric	(70)			(51)			(54)			(70)		
hemangiosarcoma, malignant, primary	1	1080	D 693	0			2	1176 1215	S 722 D 491	0		
lymph node, popliteal	(0)			(0)			(1)			(0)		

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E - Euthanized *in extremis*
D - Died on Study
( ) - Total number examined

No. - Number

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Incidences of Primary Tumors - MALE

Terminal

Tissue / Diagnosis	0 mg/kg/day			0.1 mg/kg/day			1 mg/kg/day			50 mg/kg/day		
	No. with Tumor	Animal No.	Fate/ Day	No. with Tumor	Animal No.	Fate/ Day	No. with Tumor	Animal No.	Fate/ Day	No. with Tumor	Animal No.	Fate/ Day
lymph node, renal	(0)			(2)			(0)			(0)		
mammary gland	(4)			(5)			(3)			(4)		
adenocarcinoma, malignant, primary	1	1049	E 597	0			0			0		
adenoma, benign, primary	0			1	1124	S 723	0			0		
fibroadenoma, benign, primary	2	1052	E 617	1	1107	S 722	1	1180	S 722	3	1283	S 722
		1068	S 723								1301	D 635
											1316	D 411
mesentery/peritoneum	(4)			(1)			(0)			(1)		
multicentric neoplasm	(2)			(1)			(3)			(4)		
leukemia, granulocytic, malignant, multicentric	1	1061	E 502	0			1	1237	E 352	0		
leukemia, large granular lymphocyte, malignant, multicentri	0			0			1	1228	D 403	0		
lymphoma, malignant, multicentric	0			1	1107	S 722	0			1	1257	S 722

S - Scheduled necropsy
E - Euthanized *in extremis*
D - Died on Study
( ) - Total number examined

No. - Number

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Incidences of Primary Tumors - MALE

Terminal

Tissue / Diagnosis	0 mg/kg/day No. with Tumor	Animal No.	Fate/ Day	0.1 mg/kg/day No. with Tumor	Animal No.	Fate/ Day	1 mg/kg/day No. with Tumor	Animal No.	Fate/ Day	50 mg/kg/day No. with Tumor	Animal No.	Fate/ Day
multicentric neoplasm	(2)			(1)			(3)			(4)		
sarcoma, histiocytic, malignant, multicentric	1	1037	D 628	0			1	1205	D 537	3	1258 1265 1308	D 673 D 506 E 708
nerve, sciatic	(70)			(50)			(52)			(70)		
nose, level a	(70)			(50)			(52)			(70)		
adenocarcinoma, malignant, primary	0			0			0			1	1277	S 722
nose, level b	(70)			(50)			(52)			(70)		
nose, level c	(70)			(50)			(52)			(70)		
nose, level d	(70)			(50)			(52)			(70)		
pancreas	(70)			(70)			(70)			(70)		
adenoma, acinar cell, benign, primary	0			1	1145	E 330	0			3	1267 1295 1319	D 628 S 723 S 723

S - Scheduled necropsy
E - Euthanized *in extremis*
D - Died on Study
( ) - Total number examined

No. - Number

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Incidences of Primary Tumors - MALE

Terminal

Tissue / Diagnosis	0 mg/kg/day			0.1 mg/kg/day			1 mg/kg/day			50 mg/kg/day		
	No. with Tumor	Animal No.	Fate/ Day	No. with Tumor	Animal No.	Fate/ Day	No. with Tumor	Animal No.	Fate/ Day	No. with Tumor	Animal No.	Fate/ Day
pancreas	(70)			(70)			(70)			(70)		
adenoma, islet cell, benign, primary	9	1021	E 688	9	1093	S 722	7	1188	E 602	7	1252	S 722
		1030	D 598		1105	E 651		1193	S 722		1269	E 646
		1031	S 722		1112	S 722		1200	D 679		1271	D 722
		1049	E 597		1120	S 722		1201	D 546		1294	S 723
		1050	D 596		1122	S 723		1209	E 619		1303	D 612
		1051	E 641		1123	S 723		1227	S 723		1307	D 639
		1063[r]	E 686		1156	E 569		1229	E 664		1315	S 723
		1067	S 723		1158	E 628						
		1068	S 723		1159	E 708						
carcinoma, acinar cell, malignant, primary	0			0			0			2	1280	D 722
											1301	D 635
carcinoma, islet cell, malignant, primary	1	1080	D 693	4	1109	S 722	1	1217	E 703	2	1257	S 722
					1110	E 687					1309	S 723
					1115	E 645						
					1135	D 660						

S - Scheduled necropsy
E - Euthanized *in extremis*
D - Died on Study
( ) - Total number examined

No. - Number
[r] Replacement animal

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Incidences of Primary Tumors - MALE

Terminal

Tissue / Diagnosis	0 mg/kg/day No. with Tumor	Animal No.	Fate/ Day	0.1 mg/kg/day No. with Tumor	Animal No.	Fate/ Day	1 mg/kg/day No. with Tumor	Animal No.	Fate/ Day	50 mg/kg/day No. with Tumor	Animal No.	Fate/ Day
parathyroid glands	(64)			(43)			(46)			(60)		
adenoma, benign, primary	1	1012	D 635	2	1100	D 663	0			1	1277	S 722
					1159	E 708						
carcinoma, c-cell, malignant, secondary	0			0			0			1	1254	S 722
pharynx	(70)			(49)			(52)			(69)		
papilloma, squamous cell, benign, primary	0			0			0			1	1273	E 380
pituitary gland	(70)			(52)			(60)			(70)		
adenoma, pars distalis, benign, primary	51	1011	S 722	31	1095	D 507	42	1171	S 722	46	1251	S 722
		1012	D 635		1098	D 642		1172	E 569		1252	S 722
		1013	D 663		1100	D 663		1173	E 553		1253	E 610
		1014	S 722		1101	D 388		1175	D 634		1254	S 722
		1016	E 602		1102	D 650		1176	S 722		1257	S 722
		1018	E 654		1105	E 651		1178	S 722		1258	D 673
		1019	E 547		1110	E 687		1179	D 515		1259	D 462
		1020	D 546		1115	E 645		1181	D 402		1260	D 716
		1021	E 688		1118	E 590		1182	D 450		1261	S 722

S - Scheduled necropsy
E - Euthanized *in extremis*
D - Died on Study
( ) - Total number examined

No. - Number

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Incidences of Primary Tumors - MALE

Terminal

Tissue / Diagnosis	0 mg/kg/day			0.1 mg/kg/day			1 mg/kg/day			50 mg/kg/day		
	No. with Tumor	Animal No.	Fate/ Day	No. with Tumor	Animal No.	Fate/ Day	No. with Tumor	Animal No.	Fate/ Day	No. with Tumor	Animal No.	Fate/ Day
pituitary gland	(70)			(52)			(60)			(70)		
adenoma, pars distalis, benign, primary	51	1022	D 696	31	1121	E 590	42	1183	D 537	46	1262	D 575
		1023	D 614		1124	S 723		1184	E 591		1263	E 608
		1024	E 645		1125	E 701		1185	D 552		1264	E 554
		1026	S 722		1126	E 687		1186	S 722		1265	D 506
		1027	E 439		1127	S 723		1187	D 549		1266	D 587
		1029	S 722		1128	E 553		1188	E 602		1267	D 628
		1030	D 598		1129	E 597		1189	D 462		1269	E 646
		1031	S 722		1130	E 708		1195	E 602		1270	S 722
		1032	E 458		1134	E 711		1198	E 628		1271	D 722
		1033	D 301		1135	D 660		1200	D 679		1274	E 582
		1034	E 442		1136	E 645		1201	D 546		1275	D 545
		1037	D 628		1141	D 408		1202	E 722		1276	E 596
		1039	E 714		1144	D 334		1206	E 552		1278	D 614
		1040	D 663		1146	D 527		1208	D 510		1282	E 671
		1041	S 722		1148	E 574		1209	E 619		1283	S 722
		1043	D 535		1151	E 587		1210	E 686		1285	E 432
		1044	D 307		1152	E 512		1212	S 723		1286	S 722
		1045	S 723		1154	S 723		1213	E 624		1287	S 722
		1047	E 482		1157	E 713		1215	D 491		1288	E 617
		1049	E 597		1158	E 628		1217	E 703		1290	E 569
		1050	D 596		1159	E 708		1219	D 554		1291	D 720
		1051	E 641		1160	D 651		1220	D 680		1293	D 623

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MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Incidences of Primary Tumors - MALE

Terminal

Tissue / Diagnosis	0 mg/kg/day			0.1 mg/kg/day			1 mg/kg/day			50 mg/kg/day		
	No. with Tumor	Animal No.	Fate/ Day	No. with Tumor	Animal No.	Fate/ Day	No. with Tumor	Animal No.	Fate/ Day	No. with Tumor	Animal No.	Fate/ Day
pituitary gland	(70)			(52)			(60)			(70)		
adenoma, pars distalis, benign, primary	51	1055	E 602				42	1221	S 723	46	1294	S 723
		1056	E 404					1222	D 481		1295	S 723
		1057	D 675					1224	E 475		1297	S 723
		1058	E 569					1226	E 538		1298	E 444
		1060	E 698					1227	S 723		1299	E 596
		1062	S 723					1229	E 664		1303	D 612
		1063[r]	E 686					1231	D 425		1305	E 558
		1064	D 500					1232	D 569		1307	D 639
		1065	E 577					1233	E 419		1309	S 723
		1067	S 723					1236	E 716		1311	S 723
		1068	S 723					1238	E 475		1313	E 709
		1069	D 545								1314	E 700
		1070	E 525								1315	S 723
		1071	E 708								1319	S 723
		1072	D 692								1320	E 439
		1073	E 666									
		1075	D 722									
		1078	E 611									
		1079	E 619									
		1080	D 693									

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E - Euthanized *in extremis*
D - Died on Study
( ) - Total number examined

No. - Number
[r] Replacement animal

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Incidences of Primary Tumors - MALE

Terminal

Tissue / Diagnosis	0 mg/kg/day No. with Tumor	Animal No.	Fate/ Day	0.1 mg/kg/day No. with Tumor	Animal No.	Fate/ Day	1 mg/kg/day No. with Tumor	Animal No.	Fate/ Day	50 mg/kg/day No. with Tumor	Animal No.	Fate/ Day
pituitary gland	(70)			(52)			(60)			(70)		
schwannoma, malignant, secondary	0			0			0			1	1317	E 392
preputial glands	(0)			(1)			(0)			(1)		
carcinoma, squamous cell, malignant, primary	0			1	1110	E 687	0			0		
prostate gland	(70)			(51)			(53)			(70)		
adenoma, benign, primary	1	1050	D 596	0			0			0		
salivary gland, mandibular	(70)			(49)			(52)			(69)		
salivary gland, parotid	(70)			(49)			(52)			(70)		
salivary gland, sublingual	(69)			(49)			(52)			(68)		
seminal vesicles	(70)			(50)			(53)			(70)		

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Dupont-18405-1238
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Incidences of Primary Tumors - MALE

Terminal

Tissue / Diagnosis	0 mg/kg/day			0.1 mg/kg/day			1 mg/kg/day			50 mg/kg/day		
	No. with Tumor	Animal No.	Fate/ Day	No. with Tumor	Animal No.	Fate/ Day	No. with Tumor	Animal No.	Fate/ Day	No. with Tumor	Animal No.	Fate/ Day
skeletal muscle	(0)			(0)			(1)			(0)		
skeletal muscle, biceps femoris	(70)			(50)			(52)			(70)		
skin	(70)			(58)			(58)			(70)		
adenoma, basal cell, benign, primary	0			0			1	1183	D 537	1	1257	S 722
adenoma, sebaceous cell, benign, primary	0			2	1102 1115	D 650 E 645	1	1227	S 723	0		
carcinoma, squamous cell, malignant, primary	0			3	1099 1112 1155	S 722 S 722 E 251	2	1176 1196	S 722 E 657	0		
keratoacanthoma, benign, primary	3	1035 1050 1062	S 722 D 596 S 723	6	1091 1097 1122 1123 1127 1130	S 722 S 722 S 723 S 723 S 723 E 708	5	1193 1200 1204 1223 1229	S 722 D 679 S 723 S 723 E 664	3	1257 1283 1289	S 722 S 722 S 723

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MPI Research Study Number 125-141
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Incidences of Primary Tumors - MALE

Terminal

Tissue / Diagnosis	0 mg/kg/day			0.1 mg/kg/day			1 mg/kg/day			50 mg/kg/day		
	No. with Tumor	Animal No.	Fate/ Day	No. with Tumor	Animal No.	Fate/ Day	No. with Tumor	Animal No.	Fate/ Day	No. with Tumor	Animal No.	Fate/ Day
skin	(70)			(58)			(58)			(70)		
papilloma, squamous cell, benign, primary	0			1	1115	E 645	0			2	1264	E 554
											1267	D 628
skin, subcutis	(9)			(5)			(13)			(9)		
fibroma, benign, primary	4	1016	E 602	1	1138	E 694	4	1176	S 722	5	1270	S 722
		1019	E 547					1178	S 722		1282	E 671
		1037	D 628					1193	S 722		1307	D 639
		1078	E 611					1225	S 723		1314	E 700
											1319	S 723
fibrosarcoma, malignant, primary	1	1052	E 617	1	1113	E 630	4	1188	E 602	1	1288	E 617
								1210	E 686			
								1224	E 475			
								1239	E 617			
hemangiosarcoma, malignant, primary	0			1	1156	E 569	0			0		
lipoma, benign, primary	3	1055	E 602	2	1115	E 645	2	1184	E 591	1	1296	E 407
		1058	E 569		1149	E 617		1223	S 723			
		1076	S 723									

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Incidences of Primary Tumors - MALE

Terminal

Tissue / Diagnosis	0 mg/kg/day			0.1 mg/kg/day			1 mg/kg/day			50 mg/kg/day		
	No. with Tumor	Animal No.	Fate/ Day	No. with Tumor	Animal No.	Fate/ Day	No. with Tumor	Animal No.	Fate/ Day	No. with Tumor	Animal No.	Fate/ Day
skin, subcutis	(9)			(5)			(13)			(9)		
osteosarcoma, malignant, secondary	1	1055	E 602	0			0			0		
small intestine, duodenum	(70)			(50)			(52)			(70)		
small intestine, ileum	(70)			(51)			(53)			(70)		
adenocarcinoma, malignant, primary	0			0			1	1211	S 723	0		
small intestine, jejunum	(70)			(51)			(52)			(70)		
adenocarcinoma, malignant, primary	0			2	1110	E 687	0			0		
					1125	E 701						
spinal cord, cervical	(70)			(50)			(52)			(70)		
spinal cord, lumbar	(70)			(50)			(52)			(70)		
astrocytoma, malignant, primary	1	1018	E 654	1	1130	E 708	0			0		

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Incidences of Primary Tumors - MALE

Terminal

Tissue / Diagnosis	0 mg/kg/day No. with Tumor	Animal No.	Fate/ Day	0.1 mg/kg/day No. with Tumor	Animal No.	Fate/ Day	1 mg/kg/day No. with Tumor	Animal No.	Fate/ Day	50 mg/kg/day No. with Tumor	Animal No.	Fate/ Day
spinal cord, thoracic	(70)			(50)			(52)			(70)		
astrocytoma, malignant, primary	0			0			0			1	1318	E 376
spleen	(70)			(50)			(52)			(70)		
hemangiosarcoma, malignant, primary	0			1	1157	E 713	0			0		
stomach, glandular	(70)			(50)			(53)			(70)		
stomach, nonglandular	(70)			(51)			(52)			(70)		
papilloma, squamous cell, benign, primary	1	1024	E 645	0			0			0		
tail	(0)			(1)			(0)			(0)		
testes	(70)			(70)			(70)			(70)		
adenoma, interstitial cell, benign, primary	4	1035	S 722	4	1113	E 630	1	1226	E 538	8	1260	D 716
		1055	E 602		1129	E 597					1277	S 722
		1073	E 666		1134	E 711					1288	E 617
		1076	S 723		1148	E 574					1293	D 623

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Incidences of Primary Tumors - MALE

Terminal

Tissue / Diagnosis	0 mg/kg/day No. with Tumor	Animal No.	Fate/ Day	0.1 mg/kg/day No. with Tumor	Animal No.	Fate/ Day	1 mg/kg/day No. with Tumor	Animal No.	Fate/ Day	50 mg/kg/day No. with Tumor	Animal No.	Fate/ Day
testes	(70)			(70)			(70)			(70)		
adenoma, interstitial cell, benign, primary										8	1297	S 723
											1310	E 571
											1314	E 700
											1319	S 723
hemangioma, benign, primary	0			1	1117	E 628	0			0		
mesothelioma, malignant, secondary	0			1	1128	E 553	0			0		
thymus	(69)			(50)			(52)			(68)		
thymoma, malignant, primary	1	1047	E 482	0			0			0		
thyroid gland	(70)			(51)			(53)			(70)		
adenoma, c-cell, benign, primary	7	1023	D 614	6	1121	E 590	5	1176	S 722	4	1252	S 722
		1029	S 722		1130	E 708		1185	D 552		1262	D 575
		1039	E 714		1133	D 634		1188	E 602		1282	E 671
		1040	D 663		1135	D 660		1236	E 716		1313	E 709
		1068	S 723		1157	E 713		1239	E 617			
		1075	D 722		1159	E 708						
		1076	S 723									

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Incidences of Primary Tumors - MALE

Terminal

Tissue / Diagnosis	0 mg/kg/day			0.1 mg/kg/day			1 mg/kg/day			50 mg/kg/day		
	No. with Tumor	Animal No.	Fate/ Day	No. with Tumor	Animal No.	Fate/ Day	No. with Tumor	Animal No.	Fate/ Day	No. with Tumor	Animal No.	Fate/ Day
thyroid gland	(70)			(51)			(53)			(70)		
adenoma, follicular cell, benign, primary	3	1057 1076 1077	D 675 S 723 E 722	1	1130	E 708	2	1187 1202	D 549 E 722	0		
carcinoma, c-cell, malignant, primary	1	1025	S 722	2	1093 1097	S 722 S 722	1	1202	E 722	1	1254	S 722
carcinoma, follicular cell, malignant, primary	0			0			1	1183	D 537	0		
tongue	(70)			(69)			(70)			(69)		
trachea	(70)			(50)			(52)			(70)		
ureters	(70)			(51)			(52)			(70)		
urinary bladder	(70)			(52)			(53)			(70)		

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H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Incidences of Primary Tumors - MALE

Terminal

Tissue Diagnosis	0 mg/kg/day			0.1 mg/kg/day			1 mg/kg/day			50 mg/kg/day		
	No. with Tumor	Animal No.	Fate/ Day	No. with Tumor	Animal No.	Fate/ Day	No. with Tumor	Animal No.	Fate/ Day	No. with Tumor	Animal No.	Fate/ Day
zymbal`s gland	(0)			(0)			(0)			(1)		

( ) - Total number examined
No. - Number

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Incidences of Primary Tumors - FEMALE

Terminal

Tissue / Diagnosis	0 mg/kg/day No. with Tumor	Animal No.	Fate/ Day	1 mg/kg/day No. with Tumor	Animal No.	Fate/ Day	50 mg/kg/day No. with Tumor	Animal No.	Fate/ Day	500 mg/kg/day No. with Tumor	Animal No.	Fate/ Day
adrenal glands	(70)			(70)			(70)			(70)		
adenoma, cortical, benign, primary	0			2	1456	D 590	1	1558	E 617	2	1574	E 512
					1463	E 617					1593	S 705
ganglioneuroma, benign, primary	1	1361	D 654	0			0			0		
pheochromocytoma, benign, primary	0			2	1431	S 705	1	1546	S 706	4	1577	E 607
					1435	S 705					1586	D 591
											1590	E 594
											1598	E 590
pheochromocytoma, malignant, primary	0			0			0			1	1615	D 546
aorta	(70)			(48)			(55)			(70)		
bile duct, extrahepatic	(0)			(0)			(0)			(1)		
bone	(0)			(0)			(1)			(0)		
osteosarcoma, malignant, primary	0			0			1	1505	E 593	0		

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Incidences of Primary Tumors - FEMALE

Terminal

Tissue / Diagnosis	0 mg/kg/day No. with Tumor	Animal No.	Fate/ Day	1 mg/kg/day No. with Tumor	Animal No.	Fate/ Day	50 mg/kg/day No. with Tumor	Animal No.	Fate/ Day	500 mg/kg/day No. with Tumor	Animal No.	Fate/ Day
bone marrow, femur	(70)			(48)			(55)			(70)		
bone marrow, sternum	(70)			(48)			(55)			(70)		
bone, femur	(70)			(48)			(55)			(70)		
bone, sternum	(70)			(48)			(55)			(70)		
bone, tibia	(0)			(0)			(0)			(1)		
brain	(70)			(48)			(55)			(70)		
astrocytoma, malignant, primary	1	1385	E 659	0			0			0		
carcinoma, pars distalis, malignant, secondary	5	1336	E 653	3	1426	E 579	0			0		
		1339	S 705		1439	E 681						
		1345	E 596		1457	E 568						
		1360	D 644									
		1390	E 609									

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Incidences of Primary Tumors - FEMALE

Terminal

Tissue / Diagnosis	0 mg/kg/day No. with Tumor	Animal No.	Fate/ Day	1 mg/kg/day No. with Tumor	Animal No.	Fate/ Day	50 mg/kg/day No. with Tumor	Animal No.	Fate/ Day	500 mg/kg/day No. with Tumor	Animal No.	Fate/ Day
cavity, abdominal	(0)			(1)			(0)			(2)		
adenocarcinoma, malignant, secondary	0			0			0			1	1638	E 672
mesothelioma, malignant, secondary	0			1	1451	E 644	0			0		
sarcoma, stromal, malignant, secondary	0			0			0			1	1620	E 630
cavity, thoracic	(0)			(1)			(0)			(1)		
clitoral glands	(0)			(1)			(0)			(0)		
carcinoma, squamous cell, malignant, primary	0			1	1476	D 616	0			0		
esophagus	(70)			(48)			(55)			(70)		
eyes	(69)			(48)			(55)			(70)		

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Incidences of Primary Tumors - FEMALE

Terminal

Tissue / Diagnosis	0 mg/kg/day No. with Tumor	Animal No.	Fate/ Day	1 mg/kg/day No. with Tumor	Animal No.	Fate/ Day	50 mg/kg/day No. with Tumor	Animal No.	Fate/ Day	500 mg/kg/day No. with Tumor	Animal No.	Fate/ Day
eyes, optic nerves	(69)			(48)			(55)			(70)		
eyes, retina	(62)			(43)			(53)			(65)		
galt	(69)			(48)			(55)			(68)		
harderian glands	(69)			(48)			(55)			(69)		
heart	(70)			(48)			(55)			(70)		
schwannoma, malignant, primary	0			0			1	1512	D 261	0		
joint, tibiofemoral	(70)			(48)			(55)			(70)		
kidneys	(70)			(70)			(70)			(70)		
adenocarcinoma, malignant, secondary	0			0			0			1	1638	E 672
lacrimal glands, exorbital	(69)			(48)			(55)			(70)		

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Incidences of Primary Tumors - FEMALE

Terminal

Tissue / Diagnosis	0 mg/kg/day No. with Tumor	Animal No.	Fate/ Day	1 mg/kg/day No. with Tumor	Animal No.	Fate/ Day	50 mg/kg/day No. with Tumor	Animal No.	Fate/ Day	500 mg/kg/day No. with Tumor	Animal No.	Fate/ Day
large intestine, cecum	(70)			(48)			(55)			(70)		
large intestine, colon	(70)			(48)			(55)			(70)		
large intestine, rectum	(70)			(48)			(55)			(70)		
larynx	(69)			(48)			(55)			(70)		
liver	(70)			(70)			(70)			(70)		
adenoma, hepatocellular, benign, primary	0			0			0			11	1573	E 680
											1576	S 705
											1582	E 625
											1585	S 705
											1587	S 705
											1607	S 705
											1613	S 706
											1615	D 546
											1616	D 578
											1621	S 706
											1622	D 670

S - Scheduled necropsy
E - Euthanized *in extremis*
D - Died on Study
( ) - Total number examined

No. - Number

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Incidences of Primary Tumors - FEMALE

Terminal

Tissue / Diagnosis	0 mg/kg/day No. with Tumor	Animal No.	Fate/ Day	1 mg/kg/day No. with Tumor	Animal No.	Fate/ Day	50 mg/kg/day No. with Tumor	Animal No.	Fate/ Day	500 mg/kg/day No. with Tumor	Animal No.	Fate/ Day
liver	(70)			(70)			(70)			(70)		
carcinoma, hepatocellular, malignant, primary	0			0			0			4	1599	D 577
											1607	S 705
											1608	D 526
											1615	D 546
lung	(70)			(70)			(70)			(70)		
adenocarcinoma, malignant, secondary	1	1337	E 378	0			0			2	1636	E 537
											1638	E 672
lymph node, axillary	(23)			(22)			(18)			(12)		
lymph node, hepatic	(0)			(0)			(0)			(4)		
lymph node, iliac	(1)			(4)			(3)			(7)		
lymph node, inguinal	(10)			(15)			(13)			(8)		

S - Scheduled necropsy
E - Euthanized *in extremis*
D - Died on Study
( ) - Total number examined

No. - Number

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Incidences of Primary Tumors - FEMALE

Terminal

Tissue / Diagnosis	0 mg/kg/day			1 mg/kg/day			50 mg/kg/day			500 mg/kg/day		
	No. with Tumor	Animal No.	Fate/ Day	No. with Tumor	Animal No.	Fate/ Day	No. with Tumor	Animal No.	Fate/ Day	No. with Tumor	Animal No.	Fate/ Day
lymph node, mandibular	(69)			(51)			(56)			(69)		
lymph node, mediastinal	(1)			(0)			(2)			(1)		
lymph node, mesenteric	(70)			(48)			(56)			(70)		
mammary gland	(70)			(67)			(66)			(70)		
adenocarcinoma, malignant, primary	23	1336	E 653	26	1412	E 679	23	1491	S 705	21	1573	E 680
		1337	E 378		1413	D 605		1493	D 467		1577	E 607
		1338	E 609		1416	S 705		1495	E 655		1583[r]	E 396
		1341	E 250		1419	S 705		1497	E 396		1590	E 594
		1345	E 596		1421	E 301		1502	E 700		1592	E 630
		1347	S 705		1426	E 579		1515	E 532		1600	E 694
		1352	S 705		1428	E 569		1516	S 705		1601	D 483
		1353	S 705		1429	S 705		1517	E 546		1603	E 617
		1354	E 635		1430	S 705		1518	E 174		1605	E 504
		1356	E 467		1431	S 705		1522	E 567		1606	E 476
		1357	S 705		1434	S 705		1523	E 617		1611	E 617
		1362	E 639		1437	S 706		1524	E 540		1623	S 706
		1364	E 483		1442	E 596		1525	E 523		1624	E 589
		1366	E 639		1443	E 617		1528	S 705		1626	E 588
		1373	E 357		1450	S 706		1539	E 525		1627	E 396
		1374	S 706		1451	E 644		1540	E 628		1630	D 632
		1375	E 462		1453	E 420		1541	S 706		1633	S 706

S - Scheduled necropsy
E - Euthanized *in extremis*
D - Died on Study
( ) - Total number examined

No. - Number
[r] Replacement animal

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Incidences of Primary Tumors - FEMALE

Terminal

Tissue / Diagnosis	0 mg/kg/day No. with Tumor	Animal No.	Fate/ Day	1 mg/kg/day No. with Tumor	Animal No.	Fate/ Day	50 mg/kg/day No. with Tumor	Animal No.	Fate/ Day	500 mg/kg/day No. with Tumor	Animal No.	Fate/ Day
mammary gland	(70)			(67)			(66)			(70)		
adenocarcinoma, malignant, primary	23	1376	E 604	26	1454	S 706	23	1548	E 617	21	1634	E 630
		1380	E 363		1461	E 510		1553	S 706		1636	E 537
		1384	E 638		1463	E 617		1556	E 350		1637	E 609
		1394	E 677		1464	D 554		1558	E 617		1638	E 672
		1398	E 659		1467	S 706		1559	S 706			
		1400	E 623		1470	E 439		1560	E 561			
					1473	E 644						
					1478	E 630						
					1479	E 630						
adenoma, benign, primary	4	1336	E 653	3	1446	D 479	2	1501	D 430	2	1597	E 649
		1373	E 357		1447	S 706		1550	D 635		1613	S 706
		1392	S 706		1475	S 706						
		1394	E 677									
fibroadenoma, benign, primary	34	1333	S 705	30	1413	D 605	24	1499	E 617	23	1573	E 680
		1334	E 666		1415	D 687		1502	E 700		1576	S 705
		1335	S 705		1416	S 705		1505	E 593		1579	E 609
		1336	E 653		1417	D 626		1506	D 439		1587	S 705
		1339	S 705		1418	S 705		1508	E 617		1588	E 565
		1340	E 691		1419	S 705		1509	E 645		1593	S 705
		1342	E 476		1425	S 705		1516	S 705		1598	E 590
		1345	E 596		1426	E 579		1517	E 546		1600	E 694

S - Scheduled necropsy
E - Euthanized *in extremis*
D - Died on Study
( ) - Total number examined

No. - Number

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Incidences of Primary Tumors - FEMALE

Terminal

Tissue / Diagnosis	0 mg/kg/day			1 mg/kg/day			50 mg/kg/day			500 mg/kg/day		
	No. with Tumor	Animal No.	Fate/ Day	No. with Tumor	Animal No.	Fate/ Day	No. with Tumor	Animal No.	Fate/ Day	No. with Tumor	Animal No.	Fate/ Day
mammary gland	(70)			(67)			(66)			(70)		
fibroadenoma, benign, primary	34	1346	E 407	30	1429	S 705	24	1519	E 555	23	1603	E 617
		1349	E 469		1430	S 705		1521	E 610		1604	D 403
		1351	D 495		1432	S 705		1526	E 671		1608	D 526
		1352	S 705		1434	S 705		1527	E 617		1609	D 690
		1353	S 705		1435	S 705		1531	E 596		1613	S 706
		1358	S 706		1437	S 706		1532	S 705		1616	D 578
		1360	D 644		1439	E 681		1533	E 561		1617	E 400
		1361	D 654		1440	S 706		1535	E 525		1619	E 672
		1362	E 639		1442	E 596		1538	S 705		1623	S 706
		1363	D 609		1443	E 617		1539	E 525		1624	E 589
		1366	E 639		1447	S 706		1540	E 628		1626	E 588
		1367	E 617		1449	D 516		1541	S 706		1629	D 631
		1368	S 706		1451	E 644		1549	S 706		1634	E 630
		1372	S 706		1452	E 562		1550	D 635		1636	E 537
		1373	E 357		1454	S 706		1553	S 706		1637	E 609
		1374	S 706		1456	D 590		1554	E 485			
		1376	E 604		1460	S 706						
		1382	D 557		1461	E 510						
		1383	D 550		1462	E 410						
		1385	E 659		1467	S 706						
		1389	S 706		1472	E 596						
		1390	E 609		1478	E 630						
		1392	S 706									

S - Scheduled necropsy
E - Euthanized *in extremis*
D - Died on Study
( ) - Total number examined

No. - Number

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Incidences of Primary Tumors - FEMALE

Terminal

Tissue / Diagnosis	0 mg/kg/day			1 mg/kg/day			50 mg/kg/day			500 mg/kg/day		
	No. with Tumor	Animal No.	Fate/ Day	No. with Tumor	Animal No.	Fate/ Day	No. with Tumor	Animal No.	Fate/ Day	No. with Tumor	Animal No.	Fate/ Day
mammary gland	(70)			(67)			(66)			(70)		
fibroadenoma, benign, primary	34	1393	E 610									
		1397	D 702									
		1398	E 659									
mesentery/peritoneum	(1)			(2)			(0)			(1)		
multicentric neoplasm	(1)			(0)			(4)			(0)		
lymphoma, malignant, multicentric	1	1352	S 705	0			4	1505	E 593	0		
								1508	E 617			
								1513	E 282			
								1551	E 469			
nerve, sciatic	(70)			(48)			(55)			(70)		
nose, level a	(70)			(48)			(55)			(70)		
nose, level b	(70)			(48)			(55)			(70)		

S - Scheduled necropsy
E - Euthanized *in extremis*
D - Died on Study
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MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Incidences of Primary Tumors - FEMALE

Terminal

Tissue / Diagnosis	0 mg/kg/day No. with Tumor	Animal No.	Fate/ Day	1 mg/kg/day No. with Tumor	Animal No.	Fate/ Day	50 mg/kg/day No. with Tumor	Animal No.	Fate/ Day	500 mg/kg/day No. with Tumor	Animal No.	Fate/ Day
nose, level c	(70)			(48)			(55)			(70)		
nose, level d	(70)			(48)			(55)			(70)		
ovaries	(70)			(50)			(56)			(70)		
hemangiosarcoma, malignant, primary	0			0			0			1	1634	E 630
luteoma, benign, primary	0			1	1480	E 544	0			0		
mesothelioma, malignant, primary	0			1	1451	E 644	0			0		
sex-cord/stromal tumor, malignant, primary	0			0			1	1551	E 469	0		
oviducts	(70)			(48)			(55)			(69)		
pancreas	(70)			(70)			(70)			(70)		
adenoma, islet cell, benign, primary	3	1371	E 334	2	1412	E 679	2	1515	E 532	3	1619	E 672
		1386	E 616		1450	S 706		1520	S 705		1621	S 706
		1394	E 677								1625	D 581

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E - Euthanized *in extremis*
D - Died on Study
( ) - Total number examined

No. - Number

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Incidences of Primary Tumors - FEMALE

Terminal

Tissue / Diagnosis	0 mg/kg/day			1 mg/kg/day			50 mg/kg/day			500 mg/kg/day		
	No. with Tumor	Animal No.	Fate/ Day	No. with Tumor	Animal No.	Fate/ Day	No. with Tumor	Animal No.	Fate/ Day	No. with Tumor	Animal No.	Fate/ Day
pancreas	(70)			(70)			(70)			(70)		
carcinoma, islet cell, malignant, primary	1	1335	S 705	0			0			0		
parathyroid glands	(53)			(37)			(41)			(53)		
adenoma, benign, primary	0			1	1446	D 479	0			0		
pharynx	(70)			(48)			(55)			(70)		
pituitary gland	(70)			(65)			(65)			(70)		
adenoma, pars distalis, benign, primary	53	1333	S 705	58	1411	E 400	58	1491	S 705	52	1566	D 349
		1334	E 666		1412	E 679		1492	E 515		1573	E 680
		1338	E 609		1413	D 605		1493	D 467		1574	E 512
		1340	E 691		1414	D 660		1494	E 703		1576	S 705
		1343	E 505		1415	D 687		1495	E 655		1577	E 607
		1344	E 411		1417	D 626		1496	S 705		1579	E 609
		1346	E 407		1418	S 705		1497	E 396		1580	E 352
		1347	S 705		1419	S 705		1498	E 382		1581	S 705
		1349	E 469		1422	E 540		1499	E 617		1582	E 625
		1350	D 464		1423	E 444		1500	S 705		1583[r]	E 396
		1351	D 495		1424	S 705		1501	D 430		1586	D 591

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E - Euthanized *in extremis*
D - Died on Study
( ) - Total number examined

No. - Number
[r] Replacement animal

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Incidences of Primary Tumors - FEMALE

Terminal

Tissue / Diagnosis	0 mg/kg/day			1 mg/kg/day			50 mg/kg/day			500 mg/kg/day		
	No. with Tumor	Animal No.	Fate/ Day	No. with Tumor	Animal No.	Fate/ Day	No. with Tumor	Animal No.	Fate/ Day	No. with Tumor	Animal No.	Fate/ Day
pituitary gland	(70)			(65)			(65)			(70)		
adenoma, pars distalis, benign, primary	53	1352	S 705	58	1427	D 507	58	1502	E 700	52	1587	S 705
		1353	S 705		1428	E 569		1503	E 638		1589	E 561
		1354	E 635		1429	S 705		1504	E 448		1590	E 594
		1355	S 705		1430	S 705		1505	E 593		1592	E 630
		1356	E 467		1431	S 705		1507	E 426		1593	S 705
		1357	S 705		1432	S 705		1508	E 617		1594	S 705
		1358	S 706		1433	E 544		1509	E 645		1595	S 705
		1359	E 505		1434	S 705		1510	D 474		1596	D 392
		1361	D 654		1435	S 705		1511	E 541		1597	E 649
		1362	E 639		1436	E 628		1514	E 392		1598	E 590
		1363	D 609		1437	S 706		1515	E 532		1599	D 577
		1364	E 483		1441	E 523		1517	E 546		1600	E 694
		1365	S 706		1442	E 596		1519	E 555		1602	E 591
		1366	E 639		1443	E 617		1521	E 610		1603	E 617
		1367	E 617		1445	E 385		1522	E 567		1605	E 504
		1368	S 706		1447	S 706		1523	E 617		1606	E 476
		1369	E 609		1448	D 609		1524	E 540		1607	S 705
		1372	S 706		1449	D 516		1525	E 523		1608	D 526
		1373	E 357		1450	S 706		1526	E 671		1610	E 320
		1374	S 706		1451	E 644		1527	E 617		1611	E 617
		1375	E 462		1452	E 562		1529	E 444		1613	S 706
		1376	E 604		1453	E 420		1530	E 540		1615	D 546

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MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Incidences of Primary Tumors - FEMALE

Terminal

Tissue / Diagnosis	0 mg/kg/day			1 mg/kg/day			50 mg/kg/day			500 mg/kg/day		
	No. with Tumor	Animal No.	Fate/ Day	No. with Tumor	Animal No.	Fate/ Day	No. with Tumor	Animal No.	Fate/ Day	No. with Tumor	Animal No.	Fate/ Day
pituitary gland	(70)			(65)			(65)			(70)		
adenoma, pars distalis, benign, primary	53	1377	D 399	58	1454	S 706	58	1531	E 596	52	1616	D 578
		1378	D 514		1455	D 604		1532	S 705		1617	E 400
		1379	E 455		1456	D 590		1534	D 587		1618	S 706
		1381	E 464		1458	E 275		1536	E 387		1621	S 706
		1382	D 557		1459	E 521		1537	E 574		1623	S 706
		1383	D 550		1460	S 706		1539	E 525		1624	E 589
		1384	E 638		1461	E 510		1540	E 628		1626	E 588
		1386	E 616		1462	E 410		1541	S 706		1628	S 706
		1387	E 532		1463	E 617		1542	D 317		1629	D 631
		1388	E 453		1464	D 554		1543	S 706		1630	D 632
		1389	S 706		1465	D 552		1544	E 526		1631	S 706
		1391	E 680		1466	D 211		1546	S 706		1632	S 706
		1392	S 706		1468	D 551		1547	S 706		1633	S 706
		1393	E 610		1469	S 706		1548	E 617		1634	E 630
		1394	E 677		1470	E 439		1549	S 706		1635	E 462
		1395	E 428		1471	S 706		1550	D 635		1636	E 537
		1396	E 485		1472	E 596		1551	E 469		1637	E 609
		1397	D 702		1473	E 644		1552	E 359		1638	E 672
		1398	E 659		1474	E 363		1553	S 706		1640	E 610
		1400	E 623		1475	S 706		1554	E 485			
					1476	D 616		1555	D 325			
					1477	E 607		1556	E 350			

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Incidences of Primary Tumors - FEMALE

Terminal

Tissue / Diagnosis	0 mg/kg/day			1 mg/kg/day			50 mg/kg/day			500 mg/kg/day		
	No. with Tumor	Animal No.	Fate/ Day	No. with Tumor	Animal No.	Fate/ Day	No. with Tumor	Animal No.	Fate/ Day	No. with Tumor	Animal No.	Fate/ Day
pituitary gland	(70)			(65)			(65)			(70)		
adenoma, pars distalis, benign, primary				58	1478	E 630	58	1557	E 662			
					1479	E 630		1558	E 617			
					1480	E 544		1560	E 561			
carcinoma, pars distalis, malignant, primary	5	1336	E 653	3	1426	E 579	0			0		
		1339	S 705		1439	E 681						
		1345	E 596		1457	E 568						
		1360	D 644									
		1390	E 609									
salivary gland, mandibular	(69)			(47)			(54)			(69)		
salivary gland, parotid	(69)			(48)			(54)			(70)		
salivary gland, sublingual	(69)			(47)			(54)			(68)		
skeletal muscle	(0)			(0)			(1)			(0)		

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Incidences of Primary Tumors - FEMALE

Terminal

Tissue / Diagnosis	0 mg/kg/day No. with Tumor	Animal No.	Fate/ Day	1 mg/kg/day No. with Tumor	Animal No.	Fate/ Day	50 mg/kg/day No. with Tumor	Animal No.	Fate/ Day	500 mg/kg/day No. with Tumor	Animal No.	Fate/ Day
skeletal muscle, biceps femoris	(70)			(48)			(55)			(70)		
skin	(70)			(48)			(55)			(70)		
adenoma, basal cell, benign, primary	1	1397	D 702	0			0			0		
carcinoma, squamous cell, malignant, primary	0			0			1	1539	E 525	0		
keratoacanthoma, benign, primary	0			0			0			1	1623	S 706
skin, subcutis	(6)			(4)			(2)			(4)		
fibroma, benign, primary	3	1344	E 411	2	1412	E 679	0			1	1635	E 462
		1361	D 654		1414	D 660						
		1376	E 604									
fibrosarcoma, malignant, primary	1	1390	E 609	1	1452	E 562	2	1527	E 617	2	1600	E 694
								1558	E 617		1630	D 632
schwannoma, benign, primary	1	1382	D 557	0			0			0		

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E - Euthanized *in extremis*
D - Died on Study
( ) - Total number examined

No. - Number

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H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Incidences of Primary Tumors - FEMALE

Terminal

Tissue / Diagnosis	0 mg/kg/day No. with Tumor	Animal No.	Fate/ Day	1 mg/kg/day No. with Tumor	Animal No.	Fate/ Day	50 mg/kg/day No. with Tumor	Animal No.	Fate/ Day	500 mg/kg/day No. with Tumor	Animal No.	Fate/ Day
skin, subcutis	(6)			(4)			(2)			(4)		
schwannoma, malignant, primary	0			1	1444	E 541	0			0		
small intestine, duodenum	(70)			(48)			(55)			(70)		
small intestine, ileum	(70)			(48)			(55)			(70)		
small intestine, jejunum	(70)			(48)			(55)			(70)		
spinal cord, cervical	(70)			(48)			(55)			(70)		
spinal cord, lumbar	(70)			(48)			(55)			(70)		
spinal cord, thoracic	(70)			(48)			(55)			(70)		
spleen	(70)			(48)			(57)			(70)		
stomach, glandular	(70)			(48)			(55)			(70)		
leiomyoma, benign, primary	0			0			0			1	1623	S 706

S - Scheduled necropsy
E - Euthanized *in extremis*
( ) - Total number examined
No. - Number

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Incidences of Primary Tumors - FEMALE

Terminal

Tissue / Diagnosis	0 mg/kg/day No. with Tumor	Animal No.	Fate/ Day	1 mg/kg/day No. with Tumor	Animal No.	Fate/ Day	50 mg/kg/day No. with Tumor	Animal No.	Fate/ Day	500 mg/kg/day No. with Tumor	Animal No.	Fate/ Day
stomach, nonglandular	(70)			(70)			(70)			(70)		
thymus	(68)			(48)			(55)			(67)		
thymoma, malignant, primary	1	1348	D 616	1	1433	E 544	0			0		
thyroid gland	(69)			(48)			(55)			(70)		
adenoma, c-cell, benign, primary	9	1333	S 705	3	1451	E 644	7	1505	E 593	7	1575	D 518
		1350	D 464		1452	E 562		1509	E 645		1576	S 705
		1355	S 705		1463	E 617		1523	E 617		1578	S 705
		1361	D 654					1526	E 671		1598	E 590
		1367	E 617					1537	E 574		1612	S 706
		1384	E 638					1548	E 617		1623	S 706
		1385	E 659					1560	E 561		1638	E 672
		1386	E 616									
		1394	E 677									
adenoma, follicular cell, benign, primary	0			0			0			1	1601	D 483
carcinoma, c-cell, malignant, primary	0			0			1	1557	E 662	0		

S - Scheduled necropsy
E - Euthanized *in extremis*
D - Died on Study
( ) - Total number examined

No. - Number

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Incidences of Primary Tumors - FEMALE

Terminal

Tissue / Diagnosis	0 mg/kg/day No. with Tumor	Animal No.	Fate/ Day	1 mg/kg/day No. with Tumor	Animal No.	Fate/ Day	50 mg/kg/day No. with Tumor	Animal No.	Fate/ Day	500 mg/kg/day No. with Tumor	Animal No.	Fate/ Day
thyroid gland	(69)			(48)			(55)			(70)		
carcinoma, follicular cell, malignant, primary	1	1371	E 334	1	1413	D 605	0			1	1609	D 690
tongue	(70)			(70)			(70)			(70)		
carcinoma, squamous cell, malignant, primary	0			0			0			1	1598	E 590
trachea	(70)			(48)			(55)			(70)		
ureters	(70)			(47)			(54)			(69)		
urinary bladder	(69)			(48)			(55)			(70)		
leiomyosarcoma, malignant, secondary	0			1	1465	D 552	0			0		
uterus with cervix	(70)			(70)			(70)			(70)		
adenocarcinoma, malignant, primary	0			0			1	1516	S 705	0		

S - Scheduled necropsy
E - Euthanized *in extremis*
D - Died on Study
( ) - Total number examined

No. - Number

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Incidences of Primary Tumors - FEMALE

Terminal

Tissue / Diagnosis	0 mg/kg/day No. with Tumor	Animal No.	Fate/ Day	1 mg/kg/day No. with Tumor	Animal No.	Fate/ Day	50 mg/kg/day No. with Tumor	Animal No.	Fate/ Day	500 mg/kg/day No. with Tumor	Animal No.	Fate/ Day
uterus with cervix	(70)			(70)			(70)			(70)		
carcinoma, squamous cell, malignant, primary	0			0			0			1	1573	E 680
granular cell tumor, benign, primary	2	1374	S 706	0			1	1504	E 448	1	1608	D 526
		1396	E 485									
leiomyosarcoma, malignant, primary	0			1	1465	D 552	0			0		
polyp, glandular, benign, primary	0			1	1465	D 552	0			0		
polyp, stromal, benign, primary	1	1400	E 623	2	1419	S 705	1	1494	E 703	7	1567	D 349
					1440	S 706					1576	S 705
											1626	E 588
											1628	S 706
											1629	D 631
											1631	S 706
											1638	E 672
sarcoma, stromal, malignant, primary	0			0			0			1	1620	E 630

S - Scheduled necropsy
E - Euthanized *in extremis*
D - Died on Study
( ) - Total number examined

No. - Number

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Incidences of Primary Tumors - FEMALE

Terminal

Tissue / Diagnosis	0 mg/kg/day No. with Tumor	Animal No.	Fate/ Day	1 mg/kg/day No. with Tumor	Animal No.	Fate/ Day	50 mg/kg/day No. with Tumor	Animal No.	Fate/ Day	500 mg/kg/day No. with Tumor	Animal No.	Fate/ Day
uterus with cervix	(70)			(70)			(70)			(70)		
schwannoma, malignant, primary	0			0			0			1	1616	D 578
vagina	(70)			(48)			(55)			(70)		
granular cell tumor, benign, primary	1	1383	D 550	1	1459	E 521	1	1548	E 617	1	1636	E 537
zymbal`s gland	(1)			(0)			(0)			(0)		
carcinoma, sebaceous cell, malignant, primary	1	1393	E 610	0			0			0		

E - Euthanized *in extremis*
D - Died on Study
( ) - Total number examined
No. - Number

Table 6
Summary of Tumors

MPI Research Study Number 125-141
DuPont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Summary of Tumor - MALE

Endpoint	0 mg/kg/day	0.1 mg/kg/day	1 mg/kg/day	50 mg/kg/day
Number of animals examined	70	70	70	70
Number of tumor-bearing animals	61	52	53	57
Number of animals with malignant tumors	11	24	15	18
Number of animals with benign tumors	58	47	47	52
Number of animals with multiple tumors	36	29	26	34
Number of animals with single tumors	25	23	27	23
Number of animals with multiple malignant tumors	8	19	9	13
Number of animals with multiple benign tumors	8	19	9	13
Number of animals with multicentric tumors	2	1	3	4
Total tumors	117	105	95	113
Total malignant tumors	13	27	16	19
Total benign tumors	104	78	79	94
Total multicentric tumors	2	1	3	4

MPI Research Study Number 125-141
DuPont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Summary of Tumor - FEMALE

Endpoint	0 mg/kg/day	1 mg/kg/day	50 mg/kg/day	500 mg/kg/day
Number of animals examined	70	70	70	70
Number of tumor-bearing animals	66	68	69	66
Number of animals with malignant tumors	30	32	30	29
Number of animals with benign tumors	62	65	64	64
Number of animals with multiple tumors	49	45	40	43
Number of animals with single tumors	17	23	29	23
Number of animals with multiple malignant tumors	26	29	25	27
Number of animals with multiple benign tumors	26	29	25	27
Number of animals with multicentric tumors	1	0	4	0
Total tumors	147	143	132	151
Total malignant tumors	34	35	34	34
Total benign tumors	113	108	98	117
Total multicentric tumors	1	0	4	0

Table 7
Statistical Analysis of Neoplastic Lesions

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Statistical Analysis of Neoplastic Lesions - MALE

Tissue[@] Diagnosis	0 mg/kg/day		0.1 mg/kg/day		1 mg/kg/day		50 mg/kg/day	
adrenal glands								
adenoma, cortical, benign								
Overall Rates (a)	2/70	(2.86%)	0/52	(0.00%)	1/52	(1.92%)	1/70	(1.43%)
Fisher Exact Test; P-value			0.5068		1.0000		1.0000	
Cochran - Armitage Trend Test; P-value	0.6704							
Peto Test; P-value	0.7302							
carcinoma, cortical, malignant								
Overall Rates (a)	0/70	(0.00%)	0/52	(0.00%)	0/52	(0.00%)	1/70	(1.43%)
Fisher Exact Test; P-value			1.0000		1.0000		1.0000	
Cochran - Armitage Trend Test; P-value	0.2045							
Peto Test; P-value	0.2328							
pheochromocytoma, benign								
Overall Rates (a)	12/70	(17.14%)	9/52	(17.31%)	7/52	(13.46%)	9/70	(12.86%)
Fisher Exact Test; P-value			1.0000		0.6233		0.6368	
Cochran - Armitage Trend Test; P-value	0.4073							
Peto Test; P-value	0.5741							

[@] Only includes tissues where at least 1 tumor was found in any group
(a) - Number of tumor-bearing animals/number of animals examined at site

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Statistical Analysis of Neoplastic Lesions - MALE

Tissue[@] Diagnosis	0 mg/kg/day		0.1 mg/kg/day		1 mg/kg/day		50 mg/kg/day	
adrenal glands								
pheochromocytoma, malignant								
Overall Rates (a)	1/70	(1.43%)	2/52	(3.85%)	0/52	(0.00%)	2/70	(2.86%)
Fisher Exact Test; P-value			0.5747		1.0000		1.0000	
Cochran - Armitage Trend Test; P-value	0.8487							
Peto Test; P-value	0.7158							
bone, femur								
osteosarcoma, malignant								
Overall Rates (a)	1/70	(1.43%)	0/51	(0.00%)	0/52	(0.00%)	0/70	(0.00%)
Fisher Exact Test; P-value			1.0000		1.0000		1.0000	
Cochran - Armitage Trend Test; P-value	0.2046							
Peto Test; P-value	0.2726							
bone, sternum								
lipoma, benign								
Overall Rates (a)	0/70	(0.00%)	0/50	(0.00%)	0/52	(0.00%)	1/70	(1.43%)
Fisher Exact Test; P-value			1.0000		1.0000		1.0000	
Cochran - Armitage Trend Test; P-value	0.2073							
Peto Test; P-value	0.1997							

[@] Only includes tissues where at least 1 tumor was found in any group
(a) - Number of tumor-bearing animals/number of animals examined at site

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Statistical Analysis of Neoplastic Lesions - MALE

Tissue[@] Diagnosis	0 mg/kg/day		0.1 mg/kg/day		1 mg/kg/day		50 mg/kg/day	
brain								
astrocytoma, malignant								
Overall Rates (a)	1/70	(1.43%)	4/50	(8.00%)	1/52	(1.92%)	0/70	(0.00%)
Fisher Exact Test; P-value			0.1592		1.0000		1.0000	
Cochran - Armitage Trend Test; P-value	0.2928							
Peto Test; P-value	0.3034							
epididymides								
mesothelioma, malignant								
Overall Rates (a)	0/70	(0.00%)	1/50	(2.00%)	0/52	(0.00%)	0/70	(0.00%)
Fisher Exact Test; P-value			0.4167		1.0000		1.0000	
Cochran - Armitage Trend Test; P-value	0.6708							
Peto Test; P-value	0.6497							
eyes								
melanoma, amelanotic, malignant								
Overall Rates (a)	1/68	(1.47%)	0/49	(0.00%)	0/51	(0.00%)	0/70	(0.00%)
Fisher Exact Test; P-value			1.0000		1.0000		0.4928	
Cochran - Armitage Trend Test; P-value	0.2014							
Peto Test; P-value	0.2804							

[@] Only includes tissues where at least 1 tumor was found in any group
(a) - Number of tumor-bearing animals/number of animals examined at site

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Statistical Analysis of Neoplastic Lesions - MALE

Tissue[@] Diagnosis	0 mg/kg/day		0.1 mg/kg/day		1 mg/kg/day		50 mg/kg/day	
eyes, optic nerves								
schwannoma, malignant								
Overall Rates (a)	0/70	(0.00%)	0/49	(0.00%)	0/51	(0.00%)	1/70	(1.43%)
Fisher Exact Test; P-value			1.0000		1.0000		1.0000	
Cochran - Armitage Trend Test; P-value	0.2088							
Peto Test; P-value	0.2167							
heart								
schwannoma, malignant								
Overall Rates (a)	0/70	(0.00%)	1/50	(2.00%)	0/52	(0.00%)	0/70	(0.00%)
Fisher Exact Test; P-value			0.4167		1.0000		1.0000	
Cochran - Armitage Trend Test; P-value	0.6708							
Peto Test; P-value	0.7558							
kidneys								
adenoma, tubular cell, benign								
Overall Rates (a)	2/70	(2.86%)	0/55	(0.00%)	0/53	(0.00%)	0/70	(0.00%)
Fisher Exact Test; P-value			0.5032		0.5055		0.4964	
Cochran - Armitage Trend Test; P-value	0.0710							
Peto Test; P-value	0.1176							

[@] Only includes tissues where at least 1 tumor was found in any group
(a) - Number of tumor-bearing animals/number of animals examined at site

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Statistical Analysis of Neoplastic Lesions - MALE

Tissue[@] Diagnosis	0 mg/kg/day		0.1 mg/kg/day		1 mg/kg/day		50 mg/kg/day	
kidneys								
carcinoma, tubular cell, malignant								
Overall Rates (a)	0/70	(0.00%)	2/55	(3.64%)	0/53	(0.00%)	0/70	(0.00%)
Fisher Exact Test; P-value			0.1916		1.0000		1.0000	
Cochran - Armitage Trend Test; P-value	0.5495							
Peto Test; P-value	0.6621							
liver								
adenoma, hepatocellular, benign								
Overall Rates (a)	1/70	(1.43%)	2/70	(2.86%)	1/70	(1.43%)	1/70	(1.43%)
Fisher Exact Test; P-value			1.0000		1.0000		1.0000	
Cochran - Armitage Trend Test; P-value	0.8403							
Peto Test; P-value	0.9574							
carcinoma, hepatocellular, malignant								
Overall Rates (a)	1/70	(1.43%)	0/70	(0.00%)	0/70	(0.00%)	2/70	(2.86%)
Fisher Exact Test; P-value			1.0000		1.0000		1.0000	
Cochran - Armitage Trend Test; P-value	0.4369							
Peto Test; P-value	0.4057							

[@] Only includes tissues where at least 1 tumor was found in any group
(a) - Number of tumor-bearing animals/number of animals examined at site

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Statistical Analysis of Neoplastic Lesions - MALE

Tissue[@] Diagnosis	0 mg/kg/day		0.1 mg/kg/day		1 mg/kg/day		50 mg/kg/day	
lung								
adenocarcinoma (primary site unknown), malignant								
Overall Rates (a)	0/70	(0.00%)	1/50	(2.00%)	0/53	(0.00%)	0/70	(0.00%)
Fisher Exact Test; P-value			0.4167		1.0000		1.0000	
Cochran - Armitage Trend Test; P-value	0.6690							
Peto Test; P-value	0.6497							
carcinoma, sebaceous cell (primary site unknown), malignant								
Overall Rates (a)	0/70	(0.00%)	0/50	(0.00%)	0/53	(0.00%)	1/70	(1.43%)
Fisher Exact Test; P-value			1.0000		1.0000		1.0000	
Cochran - Armitage Trend Test; P-value	0.2071							
Peto Test; P-value	0.2081							
lymph node, mesenteric								
hemangiosarcoma, malignant								
Overall Rates (a)	1/70	(1.43%)	0/51	(0.00%)	2/54	(3.70%)	0/70	(0.00%)
Fisher Exact Test; P-value			1.0000		0.5795		1.0000	
Cochran - Armitage Trend Test; P-value	0.7990							
Peto Test; P-value	0.8271							

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(a) - Number of tumor-bearing animals/number of animals examined at site

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Statistical Analysis of Neoplastic Lesions - MALE

Tissue[@] Diagnosis	0 mg/kg/day		0.1 mg/kg/day		1 mg/kg/day		50 mg/kg/day	
multicentric neoplasm								
leukemia, granulocytic, malignant								
Overall Rates (a)	1/70	(1.43%)	0/70	(0.00%)	1/70	(1.43%)	0/70	(0.00%)
Fisher Exact Test; P-value			1.0000		1.0000		1.0000	
Cochran - Armitage Trend Test; P-value	0.5263							
Peto Test; P-value	0.5472							
leukemia, large granular lymphocyte, malignant								
Overall Rates (a)	0/70	(0.00%)	0/70	(0.00%)	1/70	(1.43%)	0/70	(0.00%)
Fisher Exact Test; P-value			1.0000		1.0000		1.0000	
Cochran - Armitage Trend Test; P-value	0.6547							
Peto Test; P-value	0.6570							
lymphoma, malignant								
Overall Rates (a)	0/70	(0.00%)	1/70	(1.43%)	0/70	(0.00%)	1/70	(1.43%)
Fisher Exact Test; P-value			1.0000		1.0000		1.0000	
Cochran - Armitage Trend Test; P-value	0.5263							
Peto Test; P-value	0.4652							
sarcoma, histiocytic, malignant								
Overall Rates (a)	1/70	(1.43%)	0/70	(0.00%)	1/70	(1.43%)	3/70	(4.29%)
Fisher Exact Test; P-value			1.0000		1.0000		0.6195	
Cochran - Armitage Trend Test; P-value	0.1585							
Peto Test; P-value	0.1498							

[@] Only includes tissues where at least 1 tumor was found in any group
(a) - Number of tumor-bearing animals/number of animals examined at site

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Statistical Analysis of Neoplastic Lesions - MALE

Tissue[@] Diagnosis	0 mg/kg/day		0.1 mg/kg/day		1 mg/kg/day		50 mg/kg/day	
nose, level a								
adenocarcinoma, malignant								
Overall Rates (a)	0/70	(0.00%)	0/50	(0.00%)	0/52	(0.00%)	1/70	(1.43%)
Fisher Exact Test; P-value			1.0000		1.0000		1.0000	
Cochran - Armitage Trend Test; P-value	0.2073							
Peto Test; P-value	0.2202							
pancreas								
adenoma, acinar cell, benign								
Overall Rates (a)	0/70	(0.00%)	1/70	(1.43%)	0/70	(0.00%)	3/70	(4.29%)
Fisher Exact Test; P-value			1.0000		1.0000		0.2446	
Cochran - Armitage Trend Test; P-value	0.0721							
Peto Test; P-value	0.0503							
adenoma, acinar cell, benign / carcinoma, acinar cell, malignant								
Overall Rates (a)	0/70	(0.00%)	1/70	(1.43%)	0/70	(0.00%)	5/70	(7.14%)
Fisher Exact Test; P-value			1.0000		1.0000		0.0581	
Cochran - Armitage Trend Test; P-value	0.0099							
Peto Test; P-value	0.0065							

[@] Only includes tissues where at least 1 tumor was found in any group
(a) - Number of tumor-bearing animals/number of animals examined at site

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Statistical Analysis of Neoplastic Lesions - MALE

Tissue[@] Diagnosis	0 mg/kg/day		0.1 mg/kg/day		1 mg/kg/day		50 mg/kg/day	
pancreas								
adenoma, islet cell, benign								
Overall Rates (a)	9/70	(12.86%)	9/70	(12.86%)	7/70	(10.00%)	7/70	(10.00%)
Fisher Exact Test; P-value			1.0000		0.7914		0.7914	
Cochran - Armitage Trend Test; P-value	0.5023							
Peto Test; P-value	0.6313							
carcinoma, acinar cell, malignant								
Overall Rates (a)	0/70	(0.00%)	0/70	(0.00%)	0/70	(0.00%)	2/70	(2.86%)
Fisher Exact Test; P-value			1.0000		1.0000		0.4964	
Cochran - Armitage Trend Test; P-value	0.0573							
Peto Test; P-value	0.0571							
carcinoma, islet cell, malignant								
Overall Rates (a)	1/70	(1.43%)	4/70	(5.71%)	1/70	(1.43%)	2/70	(2.86%)
Fisher Exact Test; P-value			0.3659		1.0000		1.0000	
Cochran - Armitage Trend Test; P-value	1.0000							
Peto Test; P-value	0.8472							

[@] Only includes tissues where at least 1 tumor was found in any group
(a) - Number of tumor-bearing animals/number of animals examined at site

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Statistical Analysis of Neoplastic Lesions - MALE

Tissue[@] Diagnosis	0 mg/kg/day		0.1 mg/kg/day		1 mg/kg/day		50 mg/kg/day	
parathyroid glands								
adenoma, benign								
Overall Rates (a)	1/64	(1.56%)	2/43	(4.65%)	0/46	(0.00%)	1/60	(1.67%)
Fisher Exact Test; P-value			0.5633		1.0000		1.0000	
Cochran - Armitage Trend Test; P-value	0.6982							
Peto Test; P-value	0.8208							
pharynx								
papilloma, squamous cell, benign								
Overall Rates (a)	0/70	(0.00%)	0/49	(0.00%)	0/52	(0.00%)	1/69	(1.45%)
Fisher Exact Test; P-value			1.0000		1.0000		0.4964	
Cochran - Armitage Trend Test; P-value	0.2062							
Peto Test; P-value	0.2149							
pituitary gland								
adenoma, pars distalis, benign								
Overall Rates (a)	51/70	(72.86%)	31/52	(59.62%)	42/60	(70.00%)	46/70	(65.71%)
Fisher Exact Test; P-value			0.1719		0.8457		0.4639	
Cochran - Armitage Trend Test; P-value	0.5889							
Peto Test; P-value	0.6607							

[@] Only includes tissues where at least 1 tumor was found in any group
(a) - Number of tumor-bearing animals/number of animals examined at site

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Statistical Analysis of Neoplastic Lesions - MALE

Tissue[@] Diagnosis	0 mg/kg/day		0.1 mg/kg/day		1 mg/kg/day		50 mg/kg/day	
prostate gland								
adenoma, benign								
Overall Rates (a)	1/70	(1.43%)	0/51	(0.00%)	0/53	(0.00%)	0/70	(0.00%)
Fisher Exact Test; P-value			1.0000		1.0000		1.0000	
Cochran - Armitage Trend Test; P-value	0.2033							
Peto Test; P-value	0.1860							
skin / skin, subcutis								
adenoma, basal cell, benign								
Overall Rates (a)	0/70	(0.00%)	0/58	(0.00%)	1/59	(1.69%)	1/70	(1.43%)
Fisher Exact Test; P-value			1.0000		0.4574		1.0000	
Cochran - Armitage Trend Test; P-value	0.2217							
Onset Rate Test; P-value	0.1969							
adenoma, sebaceous cell, benign								
Overall Rates (a)	0/70	(0.00%)	2/58	(3.45%)	1/59	(1.69%)	0/70	(0.00%)
Fisher Exact Test; P-value			0.2034		0.4574		1.0000	
Cochran - Armitage Trend Test; P-value	0.8000							
Peto Test; P-value	0.7331							
Onset Rate Test; P-value	0.9689							

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MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Statistical Analysis of Neoplastic Lesions - MALE

Tissue[@] Diagnosis	0 mg/kg/day		0.1 mg/kg/day		1 mg/kg/day		50 mg/kg/day	
skin / skin, subcutis								
carcinoma, squamous cell, malignant								
Overall Rates (a)	0/70	(0.00%)	3/58	(5.17%)	2/59	(3.39%)	0/70	(0.00%)
Fisher Exact Test; P-value			0.0904		0.2072		1.0000	
Cochran - Armitage Trend Test; P-value	0.8426							
Peto Test; P-value	0.6295							
Onset Rate Test; P-value	0.7035							
fibroma, benign								
Overall Rates (a)	4/70	(5.71%)	1/58	(1.72%)	4/59	(6.78%)	5/70	(7.14%)
Fisher Exact Test; P-value			0.3763		1.0000		1.0000	
Cochran - Armitage Trend Test; P-value	0.4811							
Peto Test; P-value	0.5755							
Onset Rate Test; P-value	0.2309							
fibrosarcoma, malignant								
Overall Rates (a)	1/70	(1.43%)	1/58	(1.72%)	4/59	(6.78%)	1/70	(1.43%)
Fisher Exact Test; P-value			1.0000		0.1779		1.0000	
Cochran - Armitage Trend Test; P-value	0.6233							
Peto Test; P-value	0.5174							
Onset Rate Test; P-value	0.2851							

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Statistical Analysis of Neoplastic Lesions - MALE

Tissue[@] Diagnosis	0 mg/kg/day		0.1 mg/kg/day		1 mg/kg/day		50 mg/kg/day	
skin / skin, subcutis								
hemangiosarcoma, malignant								
Overall Rates (a)	0/70	(0.00%)	1/58	(1.72%)	0/59	(0.00%)	0/70	(0.00%)
Fisher Exact Test; P-value			0.4531		1.0000		1.0000	
Cochran - Armitage Trend Test; P-value	0.6645							
Onset Rate Test; P-value	0.6999							
keratoacanthoma, benign								
Overall Rates (a)	3/70	(4.29%)	6/58	(10.34%)	5/59	(8.47%)	3/70	(4.29%)
Fisher Exact Test; P-value			0.2980		0.4681		1.0000	
Cochran - Armitage Trend Test; P-value	0.9081							
Onset Rate Test; P-value	0.9401							
lipoma, benign								
Overall Rates (a)	3/70	(4.29%)	2/58	(3.45%)	2/59	(3.39%)	1/70	(1.43%)
Fisher Exact Test; P-value			1.0000		1.0000		0.6195	
Cochran - Armitage Trend Test; P-value	0.3503							
Onset Rate Test; P-value	0.4243							
papilloma, squamous cell, benign								
Overall Rates (a)	0/70	(0.00%)	1/58	(1.72%)	0/59	(0.00%)	2/70	(2.86%)
Fisher Exact Test; P-value			0.4531		1.0000		0.4964	
Cochran - Armitage Trend Test; P-value	0.2116							
Onset Rate Test; P-value	0.2136							

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Dupont-18405-1238
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Statistical Analysis of Neoplastic Lesions - MALE

Tissue[@] Diagnosis	0 mg/kg/day		0.1 mg/kg/day		1 mg/kg/day		50 mg/kg/day	
small intestine, ileum								
adenocarcinoma, malignant								
Overall Rates (a)	0/70	(0.00%)	0/51	(0.00%)	1/53	(1.89%)	0/70	(0.00%)
Fisher Exact Test; P-value			1.0000		0.4309		1.0000	
Cochran - Armitage Trend Test; P-value	0.6749							
Peto Test; P-value	0.6453							
small intestine, jejunum								
adenocarcinoma, malignant								
Overall Rates (a)	0/70	(0.00%)	2/51	(3.92%)	0/52	(0.00%)	0/70	(0.00%)
Fisher Exact Test; P-value			0.1756		1.0000		1.0000	
Cochran - Armitage Trend Test; P-value	0.5480							
Peto Test; P-value	0.5643							
spinal cord, lumbar								
astrocytoma, malignant								
Overall Rates (a)	1/70	(1.43%)	1/50	(2.00%)	0/52	(0.00%)	0/70	(0.00%)
Fisher Exact Test; P-value			1.0000		1.0000		1.0000	
Cochran - Armitage Trend Test; P-value	0.2303							
Peto Test; P-value	0.2815							

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Dupont-18405-1238
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Statistical Analysis of Neoplastic Lesions - MALE

Tissue[@] Diagnosis	0 mg/kg/day		0.1 mg/kg/day		1 mg/kg/day		50 mg/kg/day	
spinal cord, thoracic								
astrocytoma, malignant								
Overall Rates (a)	0/70	(0.00%)	0/50	(0.00%)	0/52	(0.00%)	1/70	(1.43%)
Fisher Exact Test; P-value			1.0000		1.0000		1.0000	
Cochran - Armitage Trend Test; P-value	0.2073							
Peto Test; P-value	0.2203							
spleen								
hemangiosarcoma, malignant								
Overall Rates (a)	0/70	(0.00%)	1/50	(2.00%)	0/52	(0.00%)	0/70	(0.00%)
Fisher Exact Test; P-value			0.4167		1.0000		1.0000	
Cochran - Armitage Trend Test; P-value	0.6708							
Peto Test; P-value	0.7558							
stomach, nonglandular								
papilloma, squamous cell, benign								
Overall Rates (a)	1/70	(1.43%)	0/51	(0.00%)	0/52	(0.00%)	0/70	(0.00%)
Fisher Exact Test; P-value			1.0000		1.0000		1.0000	
Cochran - Armitage Trend Test; P-value	0.2046							
Peto Test; P-value	0.2794							

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Statistical Analysis of Neoplastic Lesions - MALE

Tissue[@] Diagnosis	0 mg/kg/day		0.1 mg/kg/day		1 mg/kg/day		50 mg/kg/day	
testes								
adenoma, interstitial cell, benign								
Overall Rates (a)	4/70	(5.71%)	4/70	(5.71%)	1/70	(1.43%)	8/70	(11.43%)
Fisher Exact Test; P-value			1.0000		0.3659		0.3660	
Cochran - Armitage Trend Test; P-value	0.3147							
Peto Test; P-value	0.2788							
hemangioma, benign								
Overall Rates (a)	0/70	(0.00%)	1/70	(1.43%)	0/70	(0.00%)	0/70	(0.00%)
Fisher Exact Test; P-value			1.0000		1.0000		1.0000	
Cochran - Armitage Trend Test; P-value	0.6547							
Peto Test; P-value	0.6497							
thymus								
thymoma, malignant								
Overall Rates (a)	1/69	(1.45%)	0/50	(0.00%)	0/52	(0.00%)	0/68	(0.00%)
Fisher Exact Test; P-value			1.0000		1.0000		1.0000	
Cochran - Armitage Trend Test; P-value	0.2049							
Peto Test; P-value	0.1515							

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Dupont-18405-1238
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Statistical Analysis of Neoplastic Lesions - MALE

Tissue[@] Diagnosis	0 mg/kg/day		0.1 mg/kg/day		1 mg/kg/day		50 mg/kg/day	
thyroid gland								
adenoma, c-cell, benign								
Overall Rates (a)	7/70	(10.00%)	6/51	(11.76%)	5/53	(9.43%)	4/70	(5.71%)
Fisher Exact Test; P-value			0.7740		1.0000		0.5319	
Cochran - Armitage Trend Test; P-value	0.3368							
Peto Test; P-value	0.4928							
adenoma, follicular cell, benign								
Overall Rates (a)	3/70	(4.29%)	1/51	(1.96%)	2/53	(3.77%)	0/70	(0.00%)
Fisher Exact Test; P-value			0.6376		1.0000		0.2446	
Cochran - Armitage Trend Test; P-value	0.1602							
Peto Test; P-value	0.2428							
carcinoma, c-cell, malignant								
Overall Rates (a)	1/70	(1.43%)	2/51	(3.92%)	1/53	(1.89%)	1/70	(1.43%)
Fisher Exact Test; P-value			0.5723		1.0000		1.0000	
Cochran - Armitage Trend Test; P-value	0.8426							
Peto Test; P-value	0.9967							
carcinoma, follicular cell, malignant								
Overall Rates (a)	0/70	(0.00%)	0/51	(0.00%)	1/53	(1.89%)	0/70	(0.00%)
Fisher Exact Test; P-value			1.0000		0.4309		1.0000	
Cochran - Armitage Trend Test; P-value	0.6749							
Peto Test; P-value	0.7510							

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MPI Research Study Number 125-141
Dupont-18405-1238
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Statistical Analysis of Neoplastic Lesions - FEMALE

Tissue[@] Diagnosis	0 mg/kg/day		1 mg/kg/day		50 mg/kg/day		500 mg/kg/day	
adrenal glands								
adenoma, cortical, benign								
Overall Rates (a)	0/70	(0.00%)	2/70	(2.86%)	1/70	(1.43%)	2/70	(2.86%)
Fisher Exact Test; P-value			0.4964		1.0000		0.4964	
Cochran - Armitage Trend Test; P-value	0.3138							
Peto Test; P-value	0.3475							
ganglioneuroma, benign								
Overall Rates (a)	1/70	(1.43%)	0/70	(0.00%)	0/70	(0.00%)	0/70	(0.00%)
Fisher Exact Test; P-value			1.0000		1.0000		1.0000	
Cochran - Armitage Trend Test; P-value	0.1797							
Peto Test; P-value	0.1926							
pheochromocytoma, benign								
Overall Rates (a)	0/70	(0.00%)	2/70	(2.86%)	1/70	(1.43%)	4/70	(5.71%)
Fisher Exact Test; P-value			0.4964		1.0000		0.1196	
Cochran - Armitage Trend Test; P-value	0.0602							
Peto Test; P-value	0.0727							

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Statistical Analysis of Neoplastic Lesions - FEMALE

Tissue[@] Diagnosis	0 mg/kg/day		1 mg/kg/day		50 mg/kg/day		500 mg/kg/day	
adrenal glands								
pheochromocytoma, malignant								
Overall Rates (a)	0/70	(0.00%)	0/70	(0.00%)	0/70	(0.00%)	1/70	(1.43%)
Fisher Exact Test; P-value			1.0000		1.0000		1.0000	
Cochran - Armitage Trend Test; P-value	0.1797							
Peto Test; P-value	0.1592							
brain								
astrocytoma, malignant								
Overall Rates (a)	1/70	(1.43%)	0/48	(0.00%)	0/55	(0.00%)	0/70	(0.00%)
Fisher Exact Test; P-value			1.0000		1.0000		1.0000	
Cochran - Armitage Trend Test; P-value	0.2009							
Peto Test; P-value	0.2733							
heart								
schwannoma, malignant								
Overall Rates (a)	0/70	(0.00%)	0/48	(0.00%)	1/55	(1.82%)	0/70	(0.00%)
Fisher Exact Test; P-value			1.0000		0.4400		1.0000	
Cochran - Armitage Trend Test; P-value	0.6817							
Peto Test; P-value	0.6822							

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Statistical Analysis of Neoplastic Lesions - FEMALE

Tissue[@] Diagnosis	0 mg/kg/day		1 mg/kg/day		50 mg/kg/day		500 mg/kg/day	
liver								
adenoma, hepatocellular, benign								
Overall Rates (a)	0/70	(0.00%)	0/70	(0.00%)	0/70	(0.00%)	11/70	(15.71%)
Fisher Exact Test; P-value			1.0000		1.0000		0.0006	
Cochran - Armitage Trend Test; P-value	<0.0001							
Peto Test; P-value	<0.0001							
carcinoma, hepatocellular, malignant								
Overall Rates (a)	0/70	(0.00%)	0/70	(0.00%)	0/70	(0.00%)	4/70	(5.71%)
Fisher Exact Test; P-value			1.0000		1.0000		0.1196	
Cochran - Armitage Trend Test; P-value	0.0070							
Peto Test; P-value	0.0063							
mammary gland								
adenocarcinoma, malignant								
Overall Rates (a)	23/70	(32.86%)	26/67	(38.81%)	23/66	(34.85%)	21/70	(30.00%)
Fisher Exact Test; P-value			0.4818		0.8572		0.8557	
Cochran - Armitage Trend Test; P-value	0.6251							
Peto Test; P-value	0.2666							
Onset Rate Test; P-value	0.9064							

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Statistical Analysis of Neoplastic Lesions - FEMALE

Tissue[@] Diagnosis	0 mg/kg/day		1 mg/kg/day		50 mg/kg/day		500 mg/kg/day	
mammary gland								
adenoma, benign								
Overall Rates (a)	4/70	(5.71%)	3/67	(4.48%)	2/66	(3.03%)	2/70	(2.86%)
Fisher Exact Test; P-value			1.0000		0.6813		0.6806	
Cochran - Armitage Trend Test; P-value	0.3439							
Peto Test; P-value	0.0846							
Onset Rate Test; P-value	0.5415							
fibroadenoma, benign								
Overall Rates (a)	34/70	(48.57%)	30/67	(44.78%)	24/66	(36.36%)	23/70	(32.86%)
Fisher Exact Test; P-value			0.7327		0.1682		0.0850	
Cochran - Armitage Trend Test; P-value	0.0356							
Peto Test; P-value	0.4191							
Onset Rate Test; P-value	0.0040							
multicentric neoplasm								
lymphoma, malignant								
Overall Rates (a)	1/70	(1.43%)	0/70	(0.00%)	4/70	(5.71%)	0/70	(0.00%)
Fisher Exact Test; P-value			1.0000		0.3659		1.0000	
Cochran - Armitage Trend Test; P-value	0.8403							
Peto Test; P-value	0.8849							

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Statistical Analysis of Neoplastic Lesions - FEMALE

Tissue[@] Diagnosis	0 mg/kg/day		1 mg/kg/day		50 mg/kg/day		500 mg/kg/day	
ovaries								
hemangiosarcoma, malignant								
Overall Rates (a)	0/70	(0.00%)	0/50	(0.00%)	0/56	(0.00%)	1/70	(1.43%)
Fisher Exact Test; P-value			1.0000		1.0000		1.0000	
Cochran - Armitage Trend Test; P-value	0.2067							
Peto Test; P-value	0.2046							
luteoma, benign								
Overall Rates (a)	0/70	(0.00%)	1/50	(2.00%)	0/56	(0.00%)	0/70	(0.00%)
Fisher Exact Test; P-value			0.4167		1.0000		1.0000	
Cochran - Armitage Trend Test; P-value	0.6638							
Peto Test; P-value	0.6737							
mesothelioma, malignant								
Overall Rates (a)	0/70	(0.00%)	1/50	(2.00%)	0/56	(0.00%)	0/70	(0.00%)
Fisher Exact Test; P-value			0.4167		1.0000		1.0000	
Cochran - Armitage Trend Test; P-value	0.6638							
Peto Test; P-value	0.6058							
sex-cord/stromal tumor, malignant								
Overall Rates (a)	0/70	(0.00%)	0/50	(0.00%)	1/56	(1.79%)	0/70	(0.00%)
Fisher Exact Test; P-value			1.0000		0.4444		1.0000	
Cochran - Armitage Trend Test; P-value	0.6788							
Peto Test; P-value	0.6218							

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Statistical Analysis of Neoplastic Lesions - FEMALE

Tissue[@] Diagnosis	0 mg/kg/day		1 mg/kg/day		50 mg/kg/day		500 mg/kg/day	
pancreas								
adenoma, islet cell, benign								
Overall Rates (a)	3/70	(4.29%)	2/70	(2.86%)	2/70	(2.86%)	3/70	(4.29%)
Fisher Exact Test; P-value			1.0000		1.0000		1.0000	
Cochran - Armitage Trend Test; P-value	1.0000							
Peto Test; P-value	0.9819							
carcinoma, islet cell, malignant								
Overall Rates (a)	1/70	(1.43%)	0/70	(0.00%)	0/70	(0.00%)	0/70	(0.00%)
Fisher Exact Test; P-value			1.0000		1.0000		1.0000	
Cochran - Armitage Trend Test; P-value	0.1797							
Peto Test; P-value	0.1926							
parathyroid glands								
adenoma, benign								
Overall Rates (a)	0/53	(0.00%)	1/37	(2.70%)	0/41	(0.00%)	0/53	(0.00%)
Fisher Exact Test; P-value			0.4111		1.0000		1.0000	
Cochran - Armitage Trend Test; P-value	0.6661							
Peto Test; P-value	0.6286							

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Statistical Analysis of Neoplastic Lesions - FEMALE

Tissue[@] Diagnosis	0 mg/kg/day		1 mg/kg/day		50 mg/kg/day		500 mg/kg/day	
pituitary gland								
adenoma, pars distalis, benign								
Overall Rates (a)	53/70	(75.71%)	58/65	(89.23%)	58/65	(89.23%)	52/70	(74.29%)
Fisher Exact Test; P-value			0.0452		0.0452		1.0000	
Cochran - Armitage Trend Test; P-value	0.8349							
Peto Test; P-value	0.5365							
adenoma, pars distalis, benign / carcinoma, pars distalis, malignant								
Overall Rates (a)	58/70	(82.86%)	61/65	(93.85%)	58/65	(89.23%)	52/70	(74.29%)
Fisher Exact Test; P-value			0.0628		0.3297		0.3031	
Cochran - Armitage Trend Test; P-value	0.1172							
Peto Test; P-value	0.0828							
carcinoma, pars distalis, malignant								
Overall Rates (a)	5/70	(7.14%)	3/65	(4.62%)	0/65	(0.00%)	0/70	(0.00%)
Fisher Exact Test; P-value			0.7197		0.0587		0.0581	
Cochran - Armitage Trend Test; P-value	0.0045							
Peto Test; P-value	0.0067							

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Statistical Analysis of Neoplastic Lesions - FEMALE

Tissue[@] Diagnosis	0 mg/kg/day		1 mg/kg/day		50 mg/kg/day		500 mg/kg/day	
skin / skin, subcutis								
adenoma, basal cell, benign								
Overall Rates (a)	1/70	(1.43%)	0/48	(0.00%)	0/55	(0.00%)	0/70	(0.00%)
Fisher Exact Test; P-value			1.0000		1.0000		1.0000	
Cochran - Armitage Trend Test; P-value	0.2009							
Onset Rate Test; P-value	0.2345							
carcinoma, squamous cell, malignant								
Overall Rates (a)	0/70	(0.00%)	0/48	(0.00%)	1/55	(1.82%)	0/70	(0.00%)
Fisher Exact Test; P-value			1.0000		0.4400		1.0000	
Cochran - Armitage Trend Test; P-value	0.6817							
Onset Rate Test; P-value	0.7211							
fibroma, benign								
Overall Rates (a)	3/70	(4.29%)	2/48	(4.17%)	0/55	(0.00%)	1/70	(1.43%)
Fisher Exact Test; P-value			1.0000		0.2548		0.6195	
Cochran - Armitage Trend Test; P-value	0.1545							
Peto Test; P-value	0.2733							
Onset Rate Test; P-value	0.3654							

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Statistical Analysis of Neoplastic Lesions - FEMALE

Tissue[@] Diagnosis	0 mg/kg/day		1 mg/kg/day		50 mg/kg/day		500 mg/kg/day	
skin / skin, subcutis								
fibrosarcoma, malignant								
Overall Rates (a)	1/70	(1.43%)	1/48	(2.08%)	2/55	(3.64%)	2/70	(2.86%)
Fisher Exact Test; P-value			1.0000		0.5820		1.0000	
Cochran - Armitage Trend Test; P-value	0.5050							
Onset Rate Test; P-value	0.5383							
keratoacanthoma, benign								
Overall Rates (a)	0/70	(0.00%)	0/48	(0.00%)	0/55	(0.00%)	1/70	(1.43%)
Fisher Exact Test; P-value			1.0000		1.0000		1.0000	
Cochran - Armitage Trend Test; P-value	0.2096							
Onset Rate Test; P-value	0.2441							
schwannoma, benign								
Overall Rates (a)	1/70	(1.43%)	0/48	(0.00%)	0/55	(0.00%)	0/70	(0.00%)
Fisher Exact Test; P-value			1.0000		1.0000		1.0000	
Cochran - Armitage Trend Test; P-value	0.2009							
Peto Test; P-value	0.1590							
schwannoma, malignant								
Overall Rates (a)	0/70	(0.00%)	1/48	(2.08%)	0/55	(0.00%)	0/70	(0.00%)
Fisher Exact Test; P-value			0.4068		1.0000		1.0000	
Cochran - Armitage Trend Test; P-value	0.6640							
Onset Rate Test; P-value	0.6631							

[@] Only includes tissues where at least 1 tumor was found in any group
(a) - Number of tumor-bearing animals/number of animals examined at site

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Statistical Analysis of Neoplastic Lesions - FEMALE

Tissue[@] Diagnosis	0 mg/kg/day		1 mg/kg/day		50 mg/kg/day		500 mg/kg/day	
stomach, glandular								
leiomyoma, benign								
Overall Rates (a)	0/70	(0.00%)	0/48	(0.00%)	0/55	(0.00%)	1/70	(1.43%)
Fisher Exact Test; P-value			1.0000		1.0000		1.0000	
Cochran - Armitage Trend Test; P-value	0.2096							
Peto Test; P-value	0.2839							
thymus								
thymoma, malignant								
Overall Rates (a)	1/68	(1.47%)	1/48	(2.08%)	0/55	(0.00%)	0/67	(0.00%)
Fisher Exact Test; P-value			1.0000		1.0000		1.0000	
Cochran - Armitage Trend Test; P-value	0.2245							
Peto Test; P-value	0.2447							
thyroid gland								
adenoma, c-cell, benign								
Overall Rates (a)	9/69	(13.04%)	3/48	(6.25%)	7/55	(12.73%)	7/70	(10.00%)
Fisher Exact Test; P-value			0.3547		1.0000		0.6059	
Cochran - Armitage Trend Test; P-value	0.7877							
Peto Test; P-value	0.7191							

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Statistical Analysis of Neoplastic Lesions - FEMALE

Tissue[@] Diagnosis	0 mg/kg/day		1 mg/kg/day		50 mg/kg/day		500 mg/kg/day	
thyroid gland								
adenoma, follicular cell, benign								
Overall Rates (a)	0/69	(0.00%)	0/48	(0.00%)	0/55	(0.00%)	1/70	(1.43%)
Fisher Exact Test; P-value			1.0000		1.0000		1.0000	
Cochran - Armitage Trend Test; P-value	0.2109							
Peto Test; P-value	0.1623							
carcinoma, c-cell, malignant								
Overall Rates (a)	0/69	(0.00%)	0/48	(0.00%)	1/55	(1.82%)	0/70	(0.00%)
Fisher Exact Test; P-value			1.0000		0.4435		1.0000	
Cochran - Armitage Trend Test; P-value	0.6852							
Peto Test; P-value	0.7270							
carcinoma, follicular cell, malignant								
Overall Rates (a)	1/69	(1.45%)	1/48	(2.08%)	0/55	(0.00%)	1/70	(1.43%)
Fisher Exact Test; P-value			1.0000		1.0000		1.0000	
Cochran - Armitage Trend Test; P-value	0.7829							
Peto Test; P-value	0.7924							

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Statistical Analysis of Neoplastic Lesions - FEMALE

Tissue[@] Diagnosis	0 mg/kg/day		1 mg/kg/day		50 mg/kg/day		500 mg/kg/day	
tongue								
carcinoma, squamous cell, malignant								
Overall Rates (a)	0/70	(0.00%)	0/70	(0.00%)	0/70	(0.00%)	1/70	(1.43%)
Fisher Exact Test; P-value			1.0000		1.0000		1.0000	
Cochran - Armitage Trend Test; P-value	0.1797							
Peto Test; P-value	0.1866							
uterus with cervix								
adenocarcinoma, malignant								
Overall Rates (a)	0/70	(0.00%)	0/70	(0.00%)	1/70	(1.43%)	0/70	(0.00%)
Fisher Exact Test; P-value			1.0000		1.0000		1.0000	
Cochran - Armitage Trend Test; P-value	0.6547							
Peto Test; P-value	0.6422							
carcinoma, squamous cell, malignant								
Overall Rates (a)	0/70	(0.00%)	0/70	(0.00%)	0/70	(0.00%)	1/70	(1.43%)
Fisher Exact Test; P-value			1.0000		1.0000		1.0000	
Cochran - Armitage Trend Test; P-value	0.1797							
Peto Test; P-value	0.1775							

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Statistical Analysis of Neoplastic Lesions - FEMALE

Tissue[@] Diagnosis	0 mg/kg/day		1 mg/kg/day		50 mg/kg/day		500 mg/kg/day	
uterus with cervix								
granular cell tumor, benign								
Overall Rates (a)	2/70	(2.86%)	0/70	(0.00%)	1/70	(1.43%)	1/70	(1.43%)
Fisher Exact Test; P-value			0.4964		1.0000		1.0000	
Cochran - Armitage Trend Test; P-value	0.6530							
Peto Test; P-value	0.6952							
leiomyosarcoma, malignant								
Overall Rates (a)	0/70	(0.00%)	1/70	(1.43%)	0/70	(0.00%)	0/70	(0.00%)
Fisher Exact Test; P-value			1.0000		1.0000		1.0000	
Cochran - Armitage Trend Test; P-value	0.6547							
Peto Test; P-value	0.6433							
polyp, glandular, benign								
Overall Rates (a)	0/70	(0.00%)	1/70	(1.43%)	0/70	(0.00%)	0/70	(0.00%)
Fisher Exact Test; P-value			1.0000		1.0000		1.0000	
Cochran - Armitage Trend Test; P-value	0.6547							
Peto Test; P-value	0.6058							
polyp, stromal, benign								
Overall Rates (a)	1/70	(1.43%)	2/70	(2.86%)	1/70	(1.43%)	7/70	(10.00%)
Fisher Exact Test; P-value			1.0000		1.0000		0.0625	
Cochran - Armitage Trend Test; P-value	0.0196							
Peto Test; P-value	0.0201							

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Statistical Analysis of Neoplastic Lesions - FEMALE

Tissue[@] Diagnosis	0 mg/kg/day		1 mg/kg/day		50 mg/kg/day		500 mg/kg/day	
uterus with cervix								
sarcoma, stromal, malignant								
Overall Rates (a)	0/70	(0.00%)	0/70	(0.00%)	0/70	(0.00%)	1/70	(1.43%)
Fisher Exact Test; P-value			1.0000		1.0000		1.0000	
Cochran - Armitage Trend Test; P-value	0.1797							
Peto Test; P-value	0.1808							
schwannoma, malignant								
Overall Rates (a)	0/70	(0.00%)	0/70	(0.00%)	0/70	(0.00%)	1/70	(1.43%)
Fisher Exact Test; P-value			1.0000		1.0000		1.0000	
Cochran - Armitage Trend Test; P-value	0.1797							
Peto Test; P-value	0.1992							
vagina								
granular cell tumor, benign								
Overall Rates (a)	1/70	(1.43%)	1/48	(2.08%)	1/55	(1.82%)	1/70	(1.43%)
Fisher Exact Test; P-value			1.0000		1.0000		1.0000	
Cochran - Armitage Trend Test; P-value	0.9805							
Peto Test; P-value	0.9718							

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